SURGERY
Gynecology & Obstetrics
JULY 1961
VOLUME 113
NUMBER 1

# BODY FLUID DISTURBANCE RESULTING FROM PYLORIC DYSFUNCTION

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IN CONSIDERING THE PROBLEMS of fluid and electrolyte balance which may be met in surgical practice, the type and quantity of fluid required under both normal and abnormal circumstances have received much attention. Less attention, however, is usually paid to the process by which fluid normally enters the body, and it is easy to overlook the fact that ingested fluid is not metabolically available to the tissues until it has been absorbed from the alimentary tract.

When primitive life was restricted to unicellular organisms living in a saline environment, the intake and excretion of fluids took place by simple diffusion across the cell membrane, and the organism was faced by no significant osmotic challenge. Once the organisms became more complex and moved either into fresh water or onto dry land, one of the great problems they faced was to maintain constant their milieu intérieur in the face of an osmotically hostile external environment. Many solutions to this problem were evolved. One of the simplest is the contractile vacuole of the fresh water protozoa whose rate of contraction is influenced, among other stimuli, by the osmotic pressure of its environment. In man, as in many other forms of life, this problem has been solved by the development of a relatively impervious skin together with special organs of excretion. Nonetheless, to take in fluids man must still come into intimate contact with external liquids and must have a protection against the osmotic challenge of these fluids.

In effect, this contact with external liquids takes place in the small intestine. It is true that small amounts of water and electrolytes are absorbed from the stomach, but their absorption mainly takes place in the small intestine and from the viewpoint of the intake of fluids into the body, the gullet and stomach may be looked upon as a tube connecting the mouth with this absorptive area, though the passage of fluids through this tube is not automatic but is under complex control. While absorption from the intestine does not apparently depend upon simple diffusion and osmotic gradients, nonetheless the rate and direction of the net transfer of fluids across the intestinal membrane are strongly influenced by the osmotic activity of the fluid in the intestine, hyper-

The fourth Baxter Lecture presented before the Clinical Congress of the American College of Surgeons, San Francisco, 12 October 1960.
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TABLE I.—AVERAGE ELECTROLYTE CONTENT OF GASTRIC LOSS IN PYLORIC STENOSIS DUE TO DUODENAL ULCER AND PYLORIC CARCINOMA

| | *Duodenal ulcer* | *Carcinoma* |
|---|---|---|
| No. of patients | 26 | 11 |
| $Na^+$, mEq./l. | 51 | 62 |
| $K^+$, mEq./l. | 14 | 10.6 |
| $Cl^-$, mEq./l. | 122 | 58 |

From personal series and series of Lans, Stein, and Meyer (1952).

osmotic solutions causing the transfer of water into the intestine while hypo-osmotic solutions result in the passage of water from the intestine into the circulation. This effect has been clearly shown by Visscher and it is to be noted that the change in direction of net transfer occurs at about 160 millimols per liter, that is, at the concentration of the body fluids.

Rapid shifts of fluid across the intestinal membrane after eating and drinking are prevented by several factors, prominent among which is the fact that the rate of gastric emptying is strongly influenced by the osmotic activity of ingested fluids, in general the further a solution deviating from isotonicity the slower its rate of transit into the duodenum. Hunt, Macdonald, and Spurrell in 1951 and Hunt in 1956 have suggested that there are osmoreceptors in the proximal duodenum which reflexly affect the rate of gastric emptying. This in its turn depends upon the activity of the pyloric segment of the stomach, for the rate of gastric emptying depends not on the action of the pyloric sphincter itself but on the rate and depth of the peristaltic waves passing through the whole pyloric segment.

The rate of gastric emptying is, of course, affected by many factors other than the osmolarity of the ingested fluids. Furthermore, the gullet and stomach are the portal of entry into the body not only of fluids but also of solid food, and important digestive processes take place in the stomach. These are carried out by the secretion into the stomach of a highly acid juice whose main constituents are hydrochloric acid and pepsin. A normal person secretes 2 to 3 liters of decinormal hydrochloric acid into his stomach each 24 hours, and this volume is exceeded in people with duodenal ulcer. If the pylorus is obstructed, the consequent vomiting will cause a loss to the body not only of the ingested fluid and food but also of these considerable quantities of digestive juices, resulting in a serious depletion of the body fluids. If, on the other hand, the pyloric segment is removed or bypassed, the intestines are exposed to unwonted osmotic challenges, resulting in some cases in transient, but significant, postprandial dislocations of the body fluids. It is these two problems which I now intend to examine in some detail.

## PYLORIC STENOSIS

*The initial lesion.* The clinical features of pyloric stenosis are well known and require no comment, and the main interest of the condition lies in the metabolic changes resulting from the continued vomiting. The nature of these changes depends upon the pattern of the electrolyte loss, varying in detail from case to case but broadly speaking showing two patterns associated with the two common causes of pyloric obstruction in adults, namely, carcinoma of the pylorus and duodenal ulcer (Table I). In carcinoma of the pylorus, owing to the depression of acid secretion, there is an essentially equal loss of the fixed cations and anions, i.e., sodium and chloride, with no excess hydrogen ion loss. In general, this causes a simple body fluid volume deficit, often accompanied by potassium depletion and blood loss, but usually uncomplicated by any marked acid-base disturbance, and the management of such a deficit presents no special problems.

However, in stenosis due to duodenal ulcer the nature of the loss is different. Although the fluid contains significant amounts of sodium and potassium, this fixed cation loss is far exceeded by the chloride loss which represents a loss of hydrochloric acid and hence of hydrogen ions from the body. This loss leads to a disturbance of the body's acid-base balance, culminating eventually

in the condition of alkalotic tetany, with its characteristic neuromuscular irritability, sometimes accompanied by severe mental changes. The sequence of metabolic changes occurring in these patients is complex and requires careful analysis.

The initial metabolic lesion is relatively simple. In the parietal cells of the stomach dissociated carbonic acid is formed by the action of carbonic anhydrase; together with chloride, the hydrogen ions are secreted into the stomach as hydrochloric acid and hence lost in the vomit, whereas the chloride removed from the plasma is replaced by the unattached bicarbonate ion. This reaction must affect the acid-base balance of the body as a whole, and whether viewed as an addition of bicarbonate, a loss of chloride, or a removal of hydrogen ions with the carbon dioxide pressure remaining constant it must, as the loss becomes severe, result in a fall in the extracellular hydrogen ion concentration, with a titration of the buffer acids toward alkalinity—in other words, a metabolic alkalosis, with a rise in plasma *p*H, a fall in plasma chloride concentration, and a rise in the buffer anion concentration, almost entirely due to the increase in bicarbonate (Fig. 1). As would be expected, this condition is accompanied by an alkaline urine containing little or no chloride but an increased bicarbonate content. At the same time, the water depletion resulting from impaired intake and vomiting leads to a low urine volume of high specific gravity and to a rising blood urea concentration. All these changes together constitute the typical metabolic effects of early pyloric stenosis, and it is to be noted that at this stage the changes in electrolyte composition of the plasma are essentially confined to the anions.

This process by which the body responds to a metabolic alkalosis by secreting an alkaline urine is usually referred to as a renal compensation for the alkalosis, yet, as the condition progresses, the reaction of the urine changes, so that in severe pyloric

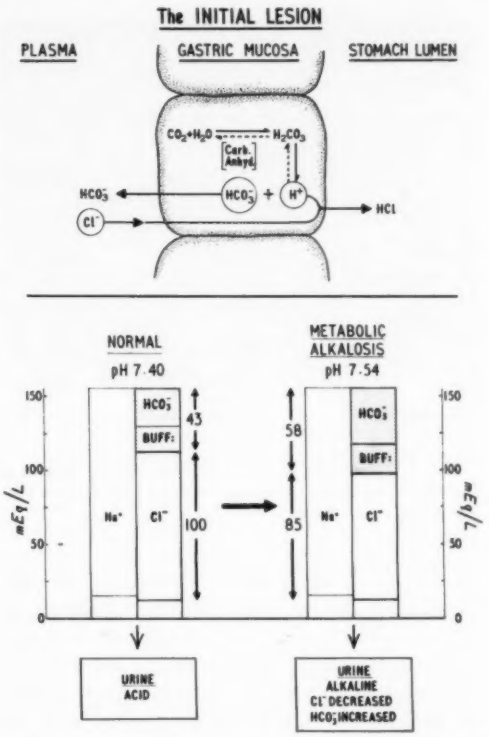


FIG. 1. Diagrammatic representation of the initial lesion in pyloric stenosis. The upper section shows the exchanges taking place in the stomach with, below, their effect on the plasma electrolytes and on the urine. As explained in the text, these plasma changes only become marked when the losses are severe and there is as well a cation deficit.

stenosis there is the apparent paradox of a severely alkalemic patient passing a highly acid urine. This condition has been recognized for many years, and its significance has received much attention. There is no doubt that in some instances the administration of normal saline restores an alkaline urine, but in others, probably the majority, this is not so. In these, saline not only fails to alkalinize the urine but also increases the alkalemia, and potassium must be given to correct the disturbance. The meaning of these two observations is in many ways different, yet considered together they emphasize the fact that the formation of an alkaline urine, that is, a urine containing significant

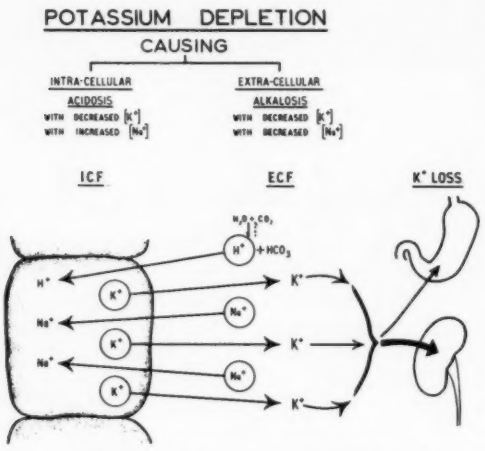


FIG. 2. Diagrammatic representation of the effects of potassium depletion in pyloric stenosis. See text for discussion of these changes.

amounts of bicarbonate, requires at the same time the secretion of fixed cations. If for any reason the cations sodium and potassium are not available to the kidneys for secretion in the urine, then the production of an alkaline urine is impossible, and in general terms it may be said that the change to an acid urine in the later stages of pyloric stenosis is due to the development of just such a situation. Further, the changes described as occurring as a result of the initial lesion only become marked when there is in addition a cation deficit. It is thus clear that, although the initial lesion is one involving anions, the part played by the cations is of great importance, and it is necessary to consider their role in the whole disturbance.

*The cation deficit.* Considering first the sodium ion, it is well established that in either metabolic or respiratory alkalosis the urinary sodium excretion is increased, and in pyloric stenosis it may continue at a high rate even in the presence of an actual sodium deficiency. Together with the sodium loss in the vomit, this urinary sodium excretion leads to a significant and increasing extracellular sodium deficit which is further accentuated by an intracellular shift of sodium discussed later. This sodium deficit results in a diminution in extracellular volume, leading in advanced cases to peripheral circulatory failure, and must stimulate an increased solution of aldosterone and other adrenocortical steroids. This increased production of adrenocortical steroids is of importance in that, in the presence of potassium depletion, it gives rise to extracellular alkalosis, thus markedly accentuating the effects of the initial lesion, *vide infra.* Further it seems likely that the changeover, as seen in the later stages of pyloric stenosis, from a urine containing increased amounts of sodium as the result of the metabolic alkalosis to one containing little or none of this cation is mainly due to the secretion of these hormones in defense of the body fluid volume. At the same time, this diminution in the urinary sodium excretion is undoubtedly a factor in the change to an acid urine, for it has been clearly shown that an alkaline urine does not occur in response to an alkalosis in sodium-depleted individuals.

Turning to the question of the potassium ion, there is no doubt that a considerable potassium deficit develops in patients with pyloric stenosis, often with a lowered serum potassium level, and further that, as in the case of sodium, although the gastric loss contributes to the deficit, it is mainly due to a high rate of renal potassium excretion which continues even in the presence of a deficit of potassium. With an extracellular alkalosis, either respiratory or metabolic in origin, the urinary excretion of potassium is increased as a result of an increased tubular secretion of the ion, and this mechanism is clearly the cause of the urinary potassium loss early in pyloric stenosis, but, as will be suggested, other causes may be at work later in the condition. However, in view of the predominantly intracellular distribution of potassium it is clear that, whatever the cause of the deficit, most of the potassium lost from the body must come from the intracellular space, thus drawing attention to a further factor

of importance in this metabolic disturbance, namely, extracellular-intracellular shifts of ions.

*Intracellular-extracellular exchanges.* The most important of these shifts are those involving the potassium ion, and their significance lies in their effect not only on the composition of the body fluids but also on renal function, for the function of the renal tubular cells, which may be regarded as specialized portions of the intracellular space, is of necessity affected by changes in the composition of the intracellular fluid, especially when these involve the relative concentrations of the potassium and hydrogen ions. The distribution of potassium between the extracellular and intracellular spaces is, among other things, influenced by the *p*H of the extracellular fluid, an extracellular alkalosis causing a shift of potassium into the cells with a fall in plasma potassium concentration, even in the presence of potassium depletion. Such an intracellular shift of potassium must take place in the metabolic alkalosis of pyloric stenosis, and it has been suggested by Scribner and associates that this is the immediate cause of the increased urinary potassium excretion.

Of greater importance, however, is the ionic shift taking place as a result of potassium depletion, which, in clinical practice is usually associated with an extracellular alkalosis. Pure potassium depletion in itself causes little or no tendency to extracellular alkalosis, but when it is accompanied by a loss of gastric juice, i.e., a loss of chloride and hydrogen ions, or a sodium excess, or increased adrenocortical steroid secretion, then a marked extracellular alkalosis develops. In clinical practice potassium depletion is often accompanied by one or more of these factors, and this is certainly the case in pyloric stenosis, especially in the later stages of the condition when the extracellular alkalosis is marked. At any rate, under these circumstances, as potassium leaves the cells it is replaced there in part by sodium and in part by hydrogen, the ratio appearing to be 2 sodium and 1 hydrogen ions entering the cells for every 3 of potassium leaving them (Fig. 2). This explains the well known observations that potassium depletion is usually accompanied by an extracellular alkalosis, an intracellular acidosis, and a rise in the intracellular sodium content. It is obvious that these changes will greatly accentuate the extracellular alkalosis occurring as a result of the initial metabolic lesion in pyloric stenosis and also increase the extracellular sodium deficit. At the same time, the alteration in the potassium-hydrogen ratio in the intracellular fluid will affect renal tubular function. Bearing in mind that the tubular secretion of hydrogen and potassium are inversely proportional, it is clear that these intracellular changes will favor the secretion of hydrogen rather than potassium, and it is probably this mechanism which is mainly responsible for the secretion of an acid urine in the later stages of pyloric stenosis.

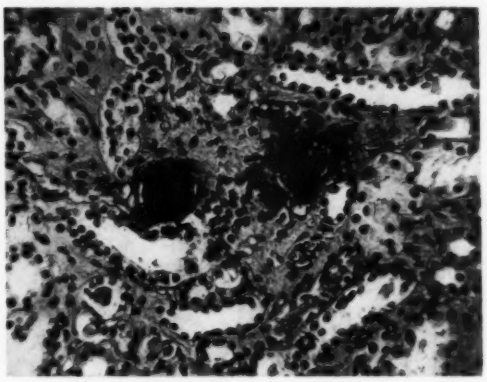

FIG. 3. Photomicrograph showing renal tubular calcification (nephrocalcinosis) from a case of pyloric stenosis. The calcium deposits are stained black. Hematoxylin and eosin, × 105.

Despite the validity of this mechanism it is important to realize that at a time when the urine is acid it still contains considerable amounts of potassium, even in the presence of a considerable potassium deficit. It seems likely that in these late stages of the condition the urinary potassium excretion is to a considerable extent due to increased adreno-

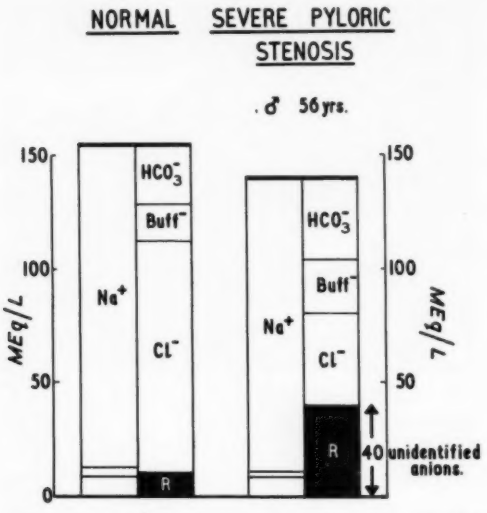


FIG. 4. The plasma composition in a patient with severe pyloric stenosis compared with the normal. The concentration of unidentified anions was 40 milliequivalents per liter, presumably largely due to the accumulation of metabolic end-products. The plasma phosphate concentration in this patient was within normal limits.

cortical steroid secretion, stimulated in part by sodium depletion and in part in response to a more general "stress" stimulus. It has been shown by Mills, Thomas, and Williamson that aldosterone and cortisol have different effects on the renal tubular secretion of potassium and hydrogen ions, and it may be that the detailed pattern of the renal loss in any individual case depends upon the exact nature of the adrenal response. Studies of the secretion of aldosterone and other adrenal steroids in severe cases of pyloric stenosis would be of interest.

The metabolic changes just described as resulting from potassium depletion can all be reversed by the administration of potassium, without the kidneys playing any part in the correction of the disturbance. Similarly, in an early case of pyloric stenosis without significant potassium depletion, Howe, Hobsley, and Le Quesne have seen the administration of normal saline correct the acid-base disturbance without the kidneys contributing to this process. It is apparent that, in theory at any rate, the whole metabolic disturbance of advanced pyloric stenosis, save only for the accumulation of urea and other metabolic end-products, could be corrected without the intervention of the kidneys. This brings up again the role of the kidneys in this condition. In the early stages, when the urine is alkaline, they are said to be compensating for the metabolic alkalosis. Considered strictly from the viewpoint of the extracellular fluid this is true, but it is apparent that this is too narrow an interpretation of their response. Rather, reflecting in their glomerular filtrate the problems of the extracellular space and in their tubular activity those of the intracellular space, as the condition develops the kidneys react to a number of stimuli with now one and then another predominating to produce a complex pattern of response. In a similar way, while classical physiologic teaching describes a respiratory compensation for a metabolic alkalosis, this fact cannot be demonstrated. To describe these apparently paradoxic responses as a failure of compensation is to misunderstand the nature of the processes occurring. The whole notion of a compensatory reaction implies that the organ or system in question is attempting to solve or to react to the problem with which it should be concerned, whereas in fact it may be responding to an entirely different stimulus. This reaction shall only be truly understood, along with other physiologic processes, when the exact stimulus has been discovered which produces the particular response observed at any given moment.

*Treatment.* Turning to the treatment of the condition, in brief it is apparent that attempts to correct the situation by the use of acidifying solutions, such as ammonium chloride, are bound to fail. What these patients need is water, sodium, potassium, and chloride and, provided these are given in adequate amounts, in most cases the tissues, lungs, and kidneys can be relied upon to use them in such a way as to correct the disturbance, an excess of any one of these being excreted by the

kidneys, which in the water now available to them also excrete the retained urea and other metabolites. These patients may present with large deficits: deficits of over 800 milliequivalents of sodium and chloride may well be present, those of up to 800 milliequivalents of potassium have been recorded by Black and Jepson, and the total water deficit may well exceed 5 liters. Large quantities of replacement fluid may therefore be required, and at least until the circulatory volume is restored these should be given rapidly. In severe cases the picture may be further complicated by an impairment of renal function with tubular calcification (Fig. 3), a lesion previously attributed to the metabolic alkalosis but which may well be due in part to the potassium depletion. Apart from the fact that it may lead to permanent renal damage, this lesion is of importance because it impairs the response of the kidneys in the acute stage and increases the accumulation of tissue metabolites, thus further distorting the composition of the body fluids. In 1 of our patients, on admission there were 40 milliequivalents per liter of unidentified anions in the plasma, presumably representing metabolic end-products (Fig. 4). To avoid these various difficulties, it is obvious that treatment should be energetic and started as soon as possible.

In addition to the replacement of the body fluid deficit, the treatment of pyloric stenosis involves many other problems, such as the emptying and cleansing of the stomach, and commonly terminates in an operation designed to restore a free passage into the intestines, a partial gastrectomy frequently being the procedure employed. The patient at once passes under the influence of the metabolic response to surgery. This phenomenon was fully described by Cuthbertson, in this Lectureship last year, and I will not discuss it beyond mentioning that with its onset the whole emphasis immediately shifts from the problem of providing adequate fluid to replace the deficits to that of restricting the intake

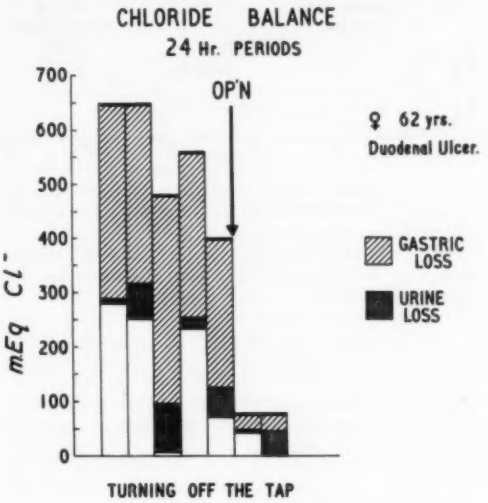


FIG. 5. Chloride balance in a patient with pyloric stenosis. Operation results in an immediate marked diminution in the losses and requirements not only of this ion but also of the other electrolytes and water.

to prevent undue retention with overloading. Whatever constituent of the intake is considered it is as though a tap has been turned off (Fig. 5), and the volume of the fluid exchanges immediately drops. In due course the patient resumes normal oral feeding, and then, as with all others after such an operation, the patient may experience symptoms as a result of the removal of the pyloric control of gastric emptying and becomes a candidate for one of the postgastrectomy syndromes.

## THE DUMPING SYNDROME

*The fall in plasma volume.* By far the most important of the postgastrectomy syndromes is the "dumping syndrome." Coming on toward the end of a meal and lasting some half to 1 hour, the symptoms of this condition are in part abdominal and in part systemic. The outstanding abdominal symptom is a feeling of distention, often accompanied by borborygmi and in severe cases by postcibal diarrhea, whereas the main systemic manifestation is fatigue with pallor, sweating, and palpitations. The

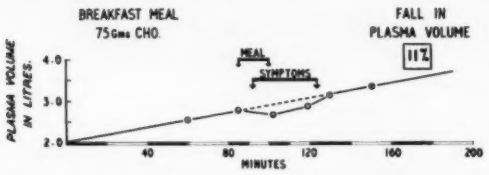


FIG. 6. Plasma volume study in a patient with the dumping syndrome, showing an 11 per cent fall in plasma volume during and after a breakfast meal containing 75 grams of carbohydrate. In this and the other studies illustrated, the plasma volume was measured by the Evans blue method.

onset of these symptoms, or fear of their onset, often restricts the patient's food intake, and the syndrome is the most important cause of weight loss after partial gastrectomy; indeed, in the less obvious examples of the condition the systemic symptoms are minimal, and the patient's only complaints are of undue distention with restriction of food intake. Characteristically, the symptoms are worst after a carbohydrate meal, are relieved by recumbency, and are most prominent in the early weeks after operation, a spontaneous improvement occurring in the majority of cases.

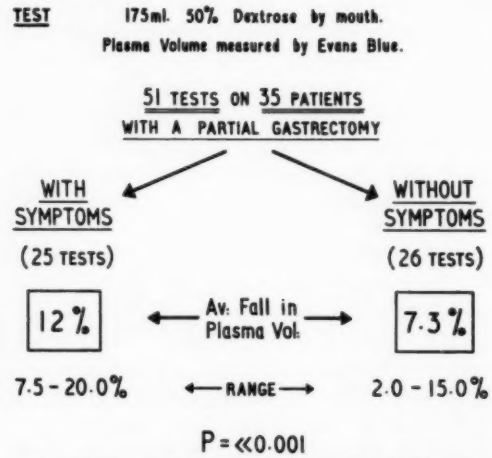


FIG. 7. Chart of plasma volume studies showing the relationship between the fall in plasma volume and the production of dumping symptoms in a series of 35 patients given oral hypertonic glucose after partial gastrectomy. Whereas the difference between the average fall in plasma volume in the two groups is significant, there is a distinct overlap.

Outstanding among the mass of experimental data concerning the syndrome is the observation that in patients with the condition the symptoms can be reproduced by the oral administration of various hypertonic solutions, in particular of hypertonic glucose. Developing this observation further, Roberts (11, 14) and her coworkers at the Memorial Hospital, New York, showed that after the administration of hypertonic solutions the symptoms were accompanied by a sharp fall in plasma volume. In the light of these findings they suggested that the dumping syndrome results from removal of the pylorus, thus allowing hypertonic solutions of ingested food to pass into the intestine where they cause an osmotic transfer of fluid from the intestine into the gut lumen, the resultant excess of fluid in the intestine giving rise to the abdominal component of the syndrome, whereas the systemic component is due to the temporary fall in plasma volume.

Since that investigation many other workers have confirmed these findings, and it has also been shown that dumping symptoms after a normal meal are accompanied by a similar fall in plasma volume (Fig. 6). However, in patients who have undergone partial gastrectomy and do not experience postcibal dumping symptoms, studies show that although in these patients oral hypertonic glucose practically never produces symptoms, it does in some produce a considerable fall in plasma volume. Our own observations have borne out this point (9). In an investigation of a group of patients with the dumping syndrome and of another group undergoing partial gastrectomy, who were studied before and at intervals after operation, it was found that in those patients who, at the time of study, were experiencing postcibal dumping symptoms, oral hypertonic glucose—175 milliliters of 50 per cent dextrose—always reproduced their symptoms and produced a significant fall in plasma volume. By contrast, in no instance did the administration of hypertonic glucose to patients without dumping

symptoms produce any significant symptoms, but the fall in plasma volume in these patients was in many instances as large as in those with symptoms. Considering the results of all our tests together (Fig. 7), the average fall in plasma volume in those with symptoms was 12 per cent and in those without 7.3 per cent. The difference between these two groups is significant, but nevertheless there is a distinct overlap between them with no clear correlation between the occurrence of symptoms and the size of the fall in plasma volume.

*The circulatory factor.* Impressed by this lack of correlation, Webber, Bender, and Moore and Duthie, Irvine, and Kerr have suggested that the fall in plasma volume is not responsible for the symptoms. However, a number of considerations make this view unlikely. Foremost among these is the change in the response to oral hypertonic glucose which takes place during the process of spontaneous recovery from the syndrome. It was my good fortune to study 2 patients who experienced severe dumping symptoms in the early weeks after operation, with marked spontaneous improvement in the ensuing months. In both patients repeated studies showed that as the postcibal symptoms lessened, so the symptoms after oral hypertonic glucose became progressively less and the fall in plasma volume progressively smaller (Fig. 8). Per contra, in 2 other patients showing no improvement in the postcibal symptoms, the response to oral hypertonic glucose remained unchanged (Fig. 9).

It seems impossible to accept that in these individual patients the relationship between the fall in plasma volume and the occurrence of symptoms was purely fortuitous. If then, it is accepted that the fall in plasma volume is responsible for the symptoms, some other factor must be found to account for the over-all lack of correlation between the two. This factor would appear to be the patient's response to a sudden fall in circulatory volume. In all our patients this response was tested by the inflation of

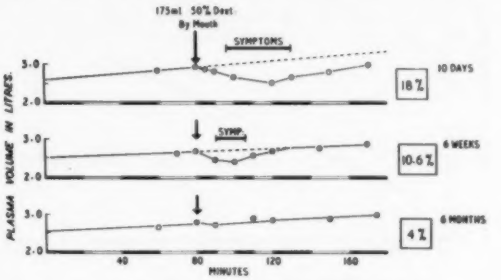


FIG. 8. Results of the repeated administration of hypertonic glucose to a patient showing spontaneous recovery from the dumping syndrome. At the time of the first test the patient was experiencing severe postprandial symptoms which gradually lessened until at 6 months postoperatively she could eat a good meal without discomfort. This improvement was accompanied by a progressive decline in the fall in plasma volume and severity of the symptoms following oral hypertonic glucose.

pneumatic cuffs around the thighs, a procedure known to produce the same effects as the venesection of some 0.5 liter of blood. Broadly speaking, this test divided our patients into two groups, those who were apparently insensitive to the procedure and those who were sensitive and reacted with changes varying from slight faintness and alteration in the pulse rate to complete collapse. Analyzing the results of the plasma volume tests in the light of these thigh-cuffing observations, it was found that in patients insensitive to a sudden reduction in circulatory volume the oral hypertonic glucose practically never produced symptoms, regardless of the size of the fall in plasma volume, whereas in those sensitive

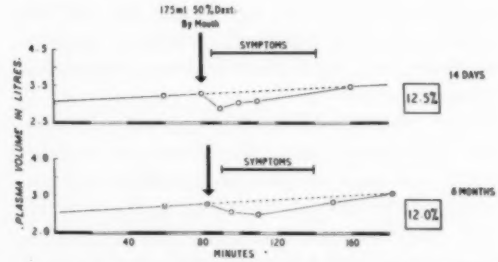


FIG. 9. Results of the repeated administration of oral hypertonic glucose to a patient whose postprandial dumping symptoms showed no improvement in 6 months after operation. Compare with Figure 8.

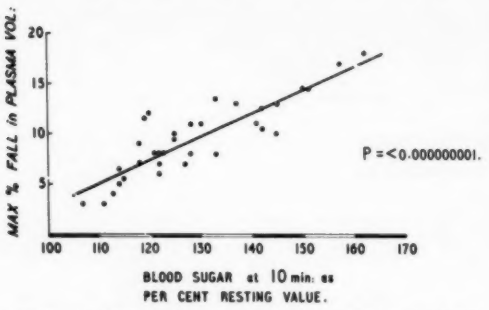


FIG. 10. Graph showing the relationship, in patients after partial gastrectomy, between the maximum fall in plasma volume and the rate of rise of the blood sugar concentration following 175 milliliters of 50 per cent dextrose by mouth. The rate of rise was calculated by expressing the blood sugar concentration 10 minutes after the ingestion of the glucose as a percentage of the resting value.

to a sudden reduction the hypertonic glucose always produced symptoms if the fall in plasma volume was 7 per cent or greater. In other words, the occurrence of symptoms depends in part on the size of the fall in plasma volume and in part on the patient's response to such a fall.

*The cause of the syndrome.* Turning to consider the cause of this fall in plasma volume, it seems certain that it is due, after the ingestion of hypertonic glucose, to an osmotic transfer of fluid into the gut lumen, for the entry of hypertonic glucose into the intestine is known to cause such a shift. Further, it seems reasonable to conclude that a similar mechanism is responsible for the fall in plasma volume occurring after normal meals in patients with the dumping syndrome. Why then should the size of this fall vary so greatly among patients who have undergone the same operation and are exposed to similar stimuli?

For many years it has been known that the dumping symptoms occur at a time when the blood sugar concentration is high and rising, and that many patients after both partial gastrectomy and gastroenterostomy have an abnormal glucose tolerance curve of the "lag" type. In the present series it was found that there was a highly significant, direct correlation between the maximum fall in plasma volume produced by the oral hypertonic glucose and the rate of rise of the blood sugar concentration, this latter being calculated by expressing the blood sugar concentration 10 minutes after the ingestion of the hypertonic glucose as a percentage of the fasting level; in other words, the greater the maximum fall in plasma volume, the faster is the rate of rise of the blood sugar concentration (Fig. 10).

The most obvious interpretation of this finding is that in those patients with a large fall in plasma volume the gastric remnant empties faster than in those with a small fall, the consequent more rapid presentation of glucose to the intestine resulting on the one hand in a more rapid absorption of glucose and hence more rapid rise in blood sugar concentration, and on the other in a more intense osmotic shift of fluid into the intestine. Put in another way, this explanation postulates that the primary factor is the rate at which the gastric remnant discharges its contents into the intestines, all the other variable changes being secondary to this. The difficulty with this interpretation is that it implies that, after partial gastrectomy, gastric evacuation is dependent upon the activity of the gastric remnant. In view of the fact that the operation removes that portion of the stomach which controls its evacuation, this seems unlikely, and in fact the available evidence suggests that after this operation gastric emptying is independent of gastric activity and depends upon jejunal peristalsis. For this and other reasons, it seems that the critical factor must be sought outside the stomach itself.

After the ingestion of glucose the shape of the blood sugar curve must depend not only on the rate of absorption of glucose from the intestine but also on its rate of removal from the blood. It may be that in patients with a rapid rise in blood sugar concentration, this rise is due not to rapid absorption but to slow removal from the blood, and that this, by interfering with

diffusion processes, results in a relatively slow absorption of glucose. This will result in sufficient glucose remaining in the intestine for a sufficient time to cause a significant fall in plasma volume, the increased fluid in the intestine in turn stimulating peristalsis, so increasing the rate of gastric emptying and setting up a vicious circle. In contrast, those patients with a slow rise of blood sugar concentration are capable of removing absorbed sugar sufficiently rapidly to allow of its continued rapid absorption so that no significant shift of fluid into the intestine occurs. In other words, this hypothesis postulates that the primary factor is the patient's ability to metabolize absorbed glucose, all the other variables, including the rate of emptying of the gastric remnant, being secondary. Further, this hypothesis postulates that spontaneous recovery from the syndrome is due to an alteration in carbohydrate metabolism, a bodily function which is known to be capable of considerable alteration in its capacities.

If there is any truth in this hypothesis it seemed possible that insulin, which is known to increase the rate of glucose utilization, might diminish the fall in plasma volume and so decrease the patient's dumping symptoms. In fact, at any rate in some cases, this appears to be true. The fall in plasma volume following a standard meal was measured in 5 patients with the dumping syndrome, and this observation was later repeated after a similar meal preceded by an appropriate dose of insulin. After the first meal all 5 patients experienced typical symptoms, but after the second these were absent, and in all cases the second meal produced a distinctly smaller fall in plasma volume than the first (Fig. 11). This observation does not of itself, of course, constitute proof of the hypothesis previously outlined which involves several assumptions which cannot be considered in detail here. Nonetheless, it is of considerable interest for two reasons, first because of its obvious therapeutic implications which are being explored and, secondly, because it focuses attention on the biochemical aspects of the dumping syndrome in place of purely mechanical considerations which have perhaps received undue attention in the past.

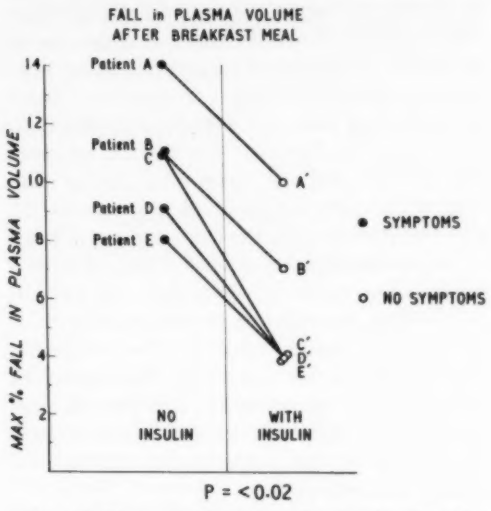


FIG. 11. Diagram of insulin studies showing the effect of a suitable adjusted, precibal injection of insulin on the fall in plasma volume and the occurrence of postprandial symptoms in 5 patients with the dumping syndrome. In each instance, after insulin the patient experienced no symptoms and the fall in plasma volume was less.

## CONCLUSION

It is likely that the final elucidation of the dumping syndrome will involve many factors of which we are as yet unaware. It is clear, however, that the essential predisposing factor must be an interference with the control of gastric emptying, a function normally exercised by the pyloric segment of the stomach, for the syndrome is only seen after the operations of total and partial gastrectomy in which this segment is excised, or after gastroenterostomy in which its controlling function is bypassed. Furthermore, the syndrome can be cured by restoration of the function of the pyloric segment by the closure of a gastroenterostomy, in those few cases in which this procedure is possible. It is sometimes stated that the

syndrome is due to destruction of the reservoir function of the stomach. It must not be forgotten, however, that to perform its functions a reservoir requires a dam and sluice gates. It has been my objective to draw attention to the fact that the pyloric segment acts at one and the same time as the dam and sluice gates of the gastric reservoir. If, as a result of disease, the free passage of fluids through this segment is obstructed, or if, as a result of a surgical operation, its normal controlling function is circumvented, then the effects spread to affect the fluid economy of the body as a whole. It is, therefore, not unreasonable to consider the pyloric segment of the stomach as one of the organs concerned in the maintenance of normal body fluid balance.

In attempting to develop this idea I have, as I am sure you are aware, drawn freely on the observations and experience of my colleagues at the Middlesex Hospital, and it is only fitting that my concluding words should be to thank them for all their help and encouragement in the work we have attempted together in the last few years.

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# PRESERVATION OF CEREBRAL CORTICAL ACTIVITY BY BREATHING OXYGEN AT TWO ATMOSPHERES OF PRESSURE DURING CEREBRAL ISCHEMIA

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ISCHEMIA is a significant factor in the morbidity and mortality from cerebral trauma and vascular accidents. The resultant cellular anoxia and death is followed by edema which in turn aggravates the ischemia. This cycle of events might be broken if anoxic cellular damage was minimized by breathing oxygen at increased pressure, thereby fully saturating hemoglobin, increasing the plasma dissolved oxygen, and increasing the diffusion gradient of this gas between capillary bed and anoxic cell.

Against this beneficial effect is the possibility of cerebral vasoconstriction which has been found by Lambertsen and his associates to follow the inhalation of oxygen rich mixtures. To test which of these two opposite effects dominates the following experiments have been carried out on 10 dogs. Each animal has acted as its own control.

## METHOD

Ten healthy mongrel dogs of body weights of 15 to 25 kilograms were anesthetized with intravenous sodium thiopentone at a dose of 25 milligrams per kilogram of body weight. The trachea was intubated with a cuffed Magill tube. Through longitudinal incisions at the root of the neck, the common carotid and the vertebral arteries were isolated and tapes were passed around each of the 4 vessels. The tapes were threaded through polythene tubes, and the snares thus formed could be used to occlude the vessels when required. Direct cortical leads to an electroencephalographic recorder were obtained by inserting silver electrodes, insulated from but carried in self-tapping brass screws which were inserted into burr holes made in the skull. Two electrodes were positioned on the left side of the brain, 3 centimeters apart and 1 centimeter from the midline. A third electrode was placed over the right side of the skull in similar manner. This served as an earth reference for the other two. The whole preparation occupied about 20 minutes. An electrocardiographic tracing was also recorded.

The method of obtaining the electroencephalogram had been tested by us on other dogs. By varying the levels of barbiturate anesthesia given by the intravenous route we found that cortical tracings, corresponding to those described by Kiersey and associates were invariably recorded. Similarly, at the end of each experiment of the present series we checked the validity of the electroencephalographic tracings by increasing the depth of anesthesia and finally sacrificing the animal. Electrocardiographic tracings were taken along with the electroencephalographic record.

Mean blood pressure tracings were obtained from the femoral artery.

After death arteriograms were made by injecting micropaque into the upper abdominal aorta with the arteries tied off at the site of test occlusion.

The 10 animals were divided into 2 groups of 5, designated A and B.

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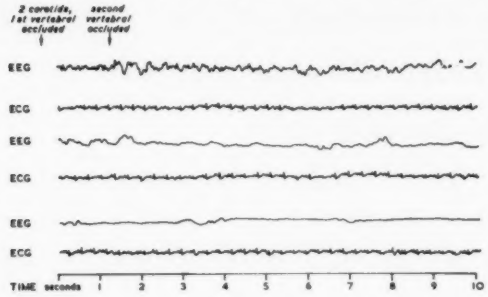


FIG. 1.

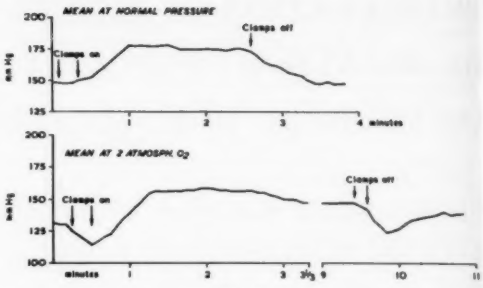


FIG. 2.

FIG. 1. Electroencephalographic and electrocardiographic records during clamping of head vessels with the animal breathing air at atmospheric pressure.

FIG. 2. Record of mean femoral artery blood pressure during carotid and vertebral artery clamping while breathing air at atmospheric pressure and oxygen at 2 atmospheres of pressure.

GROUP A

Occlusion of all 4 vessels was first carried out with the animals breathing room air. When the electroencephalographic tracing deteriorated the snares were loosened and circulation to the head was restored. The animal was then connected to a Water's soda lime cannister and rebreathing bag and allowed to breathe 100 per cent oxygen, the bag being frequently emptied and refilled from an oxygen cylinder during the ensuing half hour during which the ambient pressure was raised to the level of 2 atmospheres. At the end of this period, the 4 vessels were again closed for periods ranging from 10 to 30 minutes and the electroencephalogram recorded. After this period, the vessels were reopened, the animal was allowed to breathe air, and the ambient pressure was lowered to normal again during the ensuing 20 minutes. At this point the vessels were again shut off and the electroencephalogram was recorded.

GROUP B

The initial occlusion of the 4 neck arteries occurred while the dogs breathed oxygen at 2 atmospheres of pressure. The occlusion was maintained for periods of 10 to 30 minutes. In 4 out of the 5, the snares were loosened; in the remaining animal, occlusion of the arteries was maintained. The decompression in all dogs was begun by returning them to air breathing. The duration of the decompression was 20 minutes as before. At the end of the period, occlusion was repeated while air was breathed at normal ambient pressure.

In 2 animals of the group, before the initial closure of the arteries with the animal breathing oxygen at 2 atmospheres of pressure, blood samples were taken from the jugular vein and the femoral artery. These were repeated at intervals up to 30 minutes after arterial occlusion. They were analyzed for oxygen content by the manometric method of Van Slyke and Neil.

RESULTS

*Group A.* In 4 of the 5 animals occlusion of the arteries caused deterioration of the electroencephalographic record within a period of 15 seconds followed rapidly by loss of cortical rhythm within a period of 1 minute (Fig. 1). At this stage, the tapes were loosened; electroencephalographic rhythm returned within a period of 30 seconds rapidly reverting to the full level of activity present before occlusion. This procedure could be repeated.

On occluding the vessels at 2 atmospheres of oxygen, in the same 4 animals, only transient slowing of cortical rhythm occurred in 1 dog. No animal showed any other change in the cortical rhythm from that obtaining in the preocclusion record. This continued unchanged until the clamps were loosened

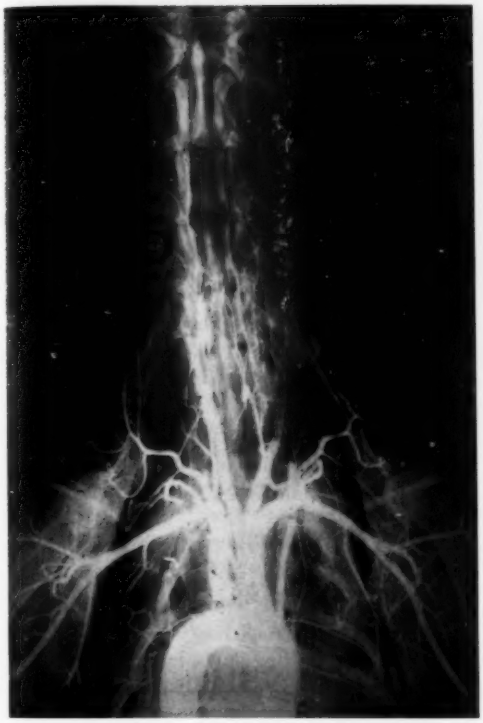

FIG. 3.

FIG. 4.

FIGS. 3 and 4. Anteroposterior and lateral arteriograms showing collateral feed into vertebral vessels distal to point of ligation in neck.

at the end of periods ranging from 10 to 30 minutes.

Repeating the procedure in these 4 dogs on return to breathing air at normal atmospheric pressure, transient slowing of activity occurred, but in only 1 did this go on to very brief cessation of cortical rhythm which returned spontaneously to control level.

In the fifth animal of this group no alteration of cortical rhythm occurred when the vessels were clamped in air or when the animal was breathing oxygen at 2 atmospheres of pressure or on return to air. In this animal, contrasting with the others of this group, the arteriographic studies showed a well developed anastomotic network between the intercostal and internal mammary arteries with the costocervical and omocervical arteries of both sides and via these to the vertebral arteries by communication with the muscular branches of this latter.

*Group B.* In all the 5 animals of this group with initial occlusion of the neck arteries while breathing oxygen at 2 atmospheres of pressure no change occurred in the cortical rhythm for the 10 to 30 minute period of occlusion. In 4 of these animals the snares were then removed, but occlusion of the vessels was maintained in the fifth dog. The animals were then returned to air breathing and decompressed. By the time normal atmospheric pressure was reached this latter animal died, apparently of cerebral anoxia. When the arteries were again occluded in the 4 other dogs no alteration in the electroencephalographic activity occurred.

The arteriovenous difference in venous return blood in the 2 animals of this group was 9.7 volumes per cent before occlusion

of head vessels with the animals breathing oxygen at 2 atmospheres of pressure, 18.9 volumes per cent 5 minutes after occlusion, and 12.6 volumes per cent 30 minutes after occlusion. It appears that the large amount of desaturation of the venous return which occurs after occlusion becomes much less marked toward the end of the period of occlusion.

The blood pressure changes when clamping both in air and oxygen at pressure are similar. These are shown in Figure 2. The increase in mean pressure which occurs after occlusion is in the region of 40 millimeters of mercury.

## DISCUSSION

It appears from these experiments that while there may be adequate collateral blood flow to maintain the vital centers, acute occlusion of the common carotid and vertebral arteries on both sides at the root of the neck gives detectable changes in the electroencephalographic cortical rhythm with complete cessation of activity when the animal is breathing air at normal pressure. When, however, the initial interruption of the circulation takes place with the animal breathing oxygen at 2 atmospheres of pressure no such change takes place. Further, it appears that exposure to high pressure oxygen for a period of 10 to 30 minutes exerts a protective effect against subsequent brain anoxia in air at normal atmospheric pressure.

The mechanism of this action appears to be twofold. In the first place, in addition to securing full saturation of the hemoglobin, at 2 atmospheres of pressure, enough oxygen is dissolved in the plasma to tide the brain over the initial postocclusion period until the second mechanism can come into play. This is the rapid opening up of collateral channels mainly between the subclavian and the brachiocephalic arteries and the vertebral vessels chiefly through the agency of the costocervical and omocervical trunks which link with the vertebral vessels through their muscular branches, as indicated in Figures 3 and 4. That this opening up of collateral pathways is rapid is confirmed by the rapid return of the large arteriovenous oxygen difference obtained after occlusion to more nearly normal levels toward the end of the period of occlusion.

The rise in the mean blood pressure levels following under perfusion of the carotid sinuses from carotid arterial occlusion would assist in the opening up of this collateral bed.

This technique may have a place in the treatment of cerebral vascular accidents and in some cases of brain injury both accidental and following definitive neurosurgical procedures.

## SUMMARY AND CONCLUSIONS

1. Occlusion of both common carotid and both vertebral arteries at the root of the neck produced loss of electroencephalographic activity in 4 out of 5 dogs breathing air at normal atmospheric pressure.

2. The same procedure but with the animals breathing oxygen at 2 atmospheres of pressure does not alter cerebral cortical activity as identified by electroencephalography.

3. The collateral channels rapidly open up and prove adequate to carry on cerebral activity if the dogs are protected by superoxygenation during the period of shutdown.

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# RESULTS OF RESECTION OF ABDOMINAL AORTIC ANEURYSM

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SINCE 1951 when the first successful resection and grafting of an abdominal aortic aneurysm was reported by Dubost and associates this method of treatment has become the preferred therapy. Many reports have appeared in the literature concerning operative technique and immediate surgical results, but relatively few studies of long term results have been compiled. It is our purpose in this article to present a series of 121 patients with abdominal aortic aneurysms treated at the Hospital of the University of Pennsylvania with follow-up on 100 per cent of the patients. The study of these patients shows that the acceptance of resection and grafting as a therapeutic measure is well founded.

## MATERIAL

From 1 June 1953 to 31 May 1960, 121 patients with abdominal aortic aneurysms were treated by surgical resection of the lesion and re-establishment of continuity of the arterial tree. This series includes all patients on whom this operation was attempted at this hospital prior to 1 June 1960. The operative procedures were performed by a total of 7 staff surgeons and 12 surgical residents, although 2 staff surgeons performed the surgery in 79 of the 121 cases. Among the 121 patients there were 92 with unruptured aortic aneurysms located distal to the renal artery. Three patients had aneurysms involving the renal arteries, and in 26 patients the aneurysm had ruptured prior to operation. It is toward the first group that the main portion of this report is directed. One hundred per cent of these 121 patients have been followed up and their present condition is known, as all patients were followed up either until their demise or until completion of this study. The 92 patients with unruptured abdominal aortic aneurysms located below the level of the renal arteries ranged in age from 31 to 79 years with an average age of 61.4 years. The 30 to 39 year age group consisted of 1 female, the 40 to 49 year group of 5 males, the 50 to 59 year group of 28 males and 1 female, the 60 to 69 year group of 42 males and 5 females, and the 70 to 79 year group of 9 males and 1 female. The majority of these patients (52 per cent) were in the decade between 60 and 69 years. Of the 92 patients, there were 84 men and 8 women; 89 of the patients were Caucasians and 3 were Negroes.

## PROCEDURE

The surgical procedure employed was excision of the aneurysm and insertion of a graft. In the early part of the series homografts were inserted in 60 patients. The vast majority of these grafts were processed by freeze drying. Sterilization was accomplished either by suspension in a penicillin and streptomycin solution, or in most cases with beta-propiolactone. Since November 1958, however, only synthetic prostheses have been used, and of these woven teflon grafts have been used predominantly. However, dacron and nylon grafts have also been employed. In 1 patient no graft was required since it was possible to achieve an end-to-end anastomosis of the aorta after excision of the aneurysm by straightening the tortuous iliac arteries.

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Supported in part by the Hartford Foundation Grant III.

TABLE I.—SURVIVAL FOLLOWING SURGERY FOR UNRUPTURED ABDOMINAL AORTIC ANEURYSM

| *Time after operation* | *No. of patients* | *No. surviving* | *Per cent* |
|---|---|---|---|
| 30 days* | 92 | 82 | 89 |
| 1 year | 71 | 57 | 80 |
| 2 years | 59 | 41 | 69 |
| 3 years | 43 | 27 | 63 |
| 4 years | 21 | 13 | 62 |
| 5 years | 13 | 8 | 62 |

*Operative period.

TABLE II.—SURVIVAL WITHOUT TREATMENT FOR UNRUPTURED ABDOMINAL ANEURYSM IN 27 PATIENTS

| *Time after diagnosis* | *No. surviving* | *Per cent* |
|---|---|---|
| 1 year | 17 | 63 |
| 2 years | 13 | 48 |
| 3 years | 9 | 33 |
| 4 years | 4 | 15 |
| 5 years | 3 | 11 |
| 6 years | 2 | 7 |
| 7 years | 2 | 7 |
| 8 years | 1 | 4 |

TABLE III.—NONFATAL COMPLICATIONS

| | | *No. of cases* |
|---|---|---|
| Cardiovascular | | 18 |
| Embolus or thrombosis of leg vessels | 11 | |
| Eventually coming to amputation | | |
| Leg 2 | | |
| Toes 1 | | |
| Thrombophlebitis of legs | 4 | |
| Cerebrovascular accident | 1 | |
| Cardiac arrest, successfully treated | 2 | |
| Acute tubular necrosis with temporary oliguria | | 4 |
| Damage to renal vein requiring nephrectomy | | 1 |
| Wound infection | | 7 |
| Moderate to severe 2 | | |
| Mild 5 | | |
| Serum hepatitis | | 3 |
| Pulmonary infection | | 2 |
| Penicillin reaction, mild, cutaneous | | 2 |
| Postoperative hemorrhage through graft | | 1 |
| Gastrointestinal hemorrhage, postoperative | | 1 |

## RESULTS

Eighty-two of the 92 patients having unruptured aneurysms survived the operative period and left the hospital. These 82 patients have now been followed up for 6 months to more than 5 years, and the results of the follow-up study are given in Table I. It can be seen that after the immediate operative mortality and an early period of high attrition, 62 per cent of those patients operated upon 5 years previously were still alive. These results are presented in Figure 1 and compared to a series of untreated patients with abdominal aneurysm previously reported from this institution by Roberts and associates. Since the time of the original report in 1957, the follow-up study has been completed. All data are presented in Table II. Within 2 years more than 50 per cent of these patients had died, at 5 years only 11 per cent remained, and at the present time there is only 1 survivor of the original 27 patients. In contrast, in the treated series 62 per cent were still living 5 years after operation. Excision and grafting has apparently effected a nearly sixfold salvage.

## OPERATIVE MORTALITY

The operative mortality, which includes all hospital deaths within 30 days of operation was 11 per cent or 10 patients among these 92. The cause of death of these 10 patients was coronary occlusion in 3, rupture of homograft in 2, renal failure in 1, pulmonary embolus in 1, and operative hemorrhage in 3. The most common postoperative complication leading to an operative death was an acute coronary occlusion. This fatal complication occurred in 3 patients between the second and seventh postoperative day. Two of the 3 patients had had 1 or more previous myocardial infarcts. In 2 of the 3 patients the coronary occlusion occurred after a relatively stormy postoperative course, 1 of the patients having had a period of hypotension leading to an oliguric phase and a postoperative femoral embolus and the other having had a severe gastrointestinal hemorrhage. The third patient, however, had done well until the seventh postoperative day when the coronary occlusion occurred. This patient had had 2 previous myocardial infarctions.

Two patients died because of rupture of the grafts. The rupture of the homografts occurred in two markedly different fashions. One graft ruptured very promptly after surgery, while the patient was still in the recovery room, and although reoperation was undertaken a clotting deficiency developed and the patient died as a result of hemorrhage. The other rupture occurred

on the twenty-eighth postoperative day, and the graft was found to have split longitudinally for a distance of 3½ centimeters along its anterior surface. It is believed that this split was due to improper reconstitution of the graft at operation. This type of death has not been seen since the use of synthetic grafts.

Although 3 of the 10 patients who died had some degree of acute tubular necrosis when examined at autopsy, only 1 man's death was attributed directly to this cause. This patient had had a lengthy operative procedure in which "oozing" had been prominent and in which there was a prolonged period of hypotension. He died on the sixth postoperative day of uremia.

Three patients died of hemorrhage from sources other than the graft itself. One of these was a 31 year old woman with surprisingly extensive atherosclerosis. She died because of operative injury to the vena cava. The remaining 2 patients died after long operative procedures characterized by massive blood replacement and uncontrolled bleeding from raw surfaces. Both of these patients were subjected to reoperation in the hope of controlling the bleeding but neither survived.

One patient, actually the first in this series, died on the ninth postoperative day of a pulmonary embolus. He had complained of mild calf tenderness earlier that day but otherwise had no complications.

### NONFATAL COMPLICATIONS

Nonfatal complications in these 92 patients operated upon for unruptured aneurysms are summarized in Table III. The most common complication, and the major complication specifically related to this type of surgery, was unquestionably arterial embolus or thrombosis in the leg. In 11 patients clinical evidence of occlusion of the femoral or popliteal artery developed in the early postoperative period. Ten of these patients were reoperated upon in an effort to restore flow to the affected limb. The other patient was considered too ill for a secondary

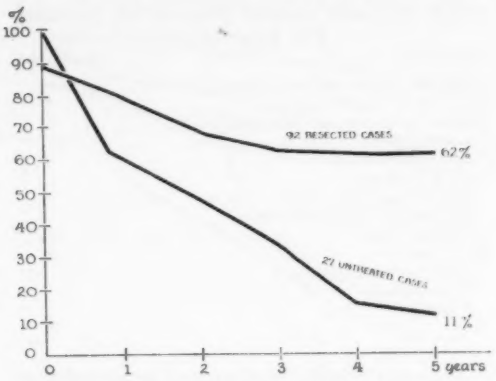


FIG. 1. Comparative survival rates of a series of patients with unruptured abdominal aortic aneurysms subjected to resection, and a series with aneurysms which were untreated. Both series are from the Hospital of the University of Pennsylvania. The resected series includes operative mortality and late deaths.

procedure and was thought to have barely adequate collateral flow. Although this patient did not regain peripheral pulses his leg appeared viable at the time of his death from myocardial infarction on the seventh postoperative day. The 10 patients subjected to reoperation included 2 in whom bilateral popliteal embolectomies were carried out. The site of the embolus was in the popliteal artery in 6 patients, in the popliteal and femoral arteries in 2 patients, and in the femoral in the remainder. The embolus or thrombus was found and removed in all patients subjected to embolectomy except 1 in whom it had lodged in the anterior tibial artery distal to the popliteal. The anterior tibial unfortunately had been the only distal artery open in his leg preoperatively, and as a result of its occlusion he ultimately lost the tips of four toes. Two other patients subsequently lost the involved limb; although 1 of these patients had had temporary restoration of peripheral pulses after the embolectomy, a secondary thrombosis or further occlusion ultimately developed. Of the 12 legs in which embolectomies were performed, pedal pulses were palpable prior to surgery in 11, and in 8 pulses were permanently restored.

TABLE IV—LATE DEATHS FOLLOWING SUCCESSFUL RESECTION

| *Cause of death* | | *No. of deaths* |
|---|---|---|
| Homograft failure with hemorrhage | | 1 |
| Suspected homograft failure | | 2 |
| Leaking suture line with infection | | 1 |
| Cardiovascular | | 10 |
| Coronary occlusion | 4 | |
| Cardiac failure | 1 | |
| Cerebrovascular accident | 3 | |
| Rupture of a second aneurysm | 2 | |
| Malignant tumors | | 2 |
| Miscellaneous | | 5 |
| Gastrointestinal bleeding | 2 | |
| Nephrosclerosis | 1 | |
| Unknown | 2 | |
| Total | | 21 |

Postoperatively, evidence of acute tubular necrosis with temporary oliguria developed in 4 of the 92 patients. All of these followed operations in which there was prolonged hypotension. None of these patients required dialysis and all recovered satisfactory renal function after conservative fluid and electrolyte management.

The remaining complications were of such type as might occur after any major surgical procedure and are summarized for completeness in Table III.

## LATE DEATHS

The late deaths in 82 patients whose aneurysms were successfully resected are tabulated in Table IV. There were 3 patients whose late deaths were attributed to rupture of a homograft or failure of a suture line. One of these patients returned to the hospital 8 months after the insertion of a homograft and the anterior superior portion of the graft was found to have ruptured. She did not survive the operative attempt to replace the graft. The two other patients in the group died at 33 days and 7 months postoperatively, and the clinical impression of the attending physician at the time of death in both cases was one of intra-abdominal hemorrhage presumably due to rupture of the graft or leak at the suture line. However, autopsies were not performed. Another patient returned to the hospital shortly after discharge because of recurrent left lower quadrant abdominal pain. Clinically, it was thought there was leaking from the area of the graft. At reoperation infection was encountered at the proximal suture line from which there had been some leak of blood. It was not believed that this represented a true failure of the graft but rather an inevitable result of infection involving the graft. It demonstrates the extreme gravity of infection in vascular surgery. Although another graft was inserted the patient subsequently succumbed because of repeated breakdown of the suture line.

There were 3 known failures in the 60 patients with homografts, making the failure rate 5 per cent. If the 2 suspected cases are added, the rate becomes 8.3 per cent.

The 10 late deaths attributable to cardiovascular disease emphasize the fact that these patients usually have extensive arteriosclerotic changes throughout the vascular system. Two patients died of a rupture of a second aneurysm. One of these died more than 4 years after removal of an abdominal aneurysm when dissection of the aorta occurred from the left carotid artery to the proximal suture line of the abdominal graft at which point dissection broke into the retroperitoneal space. The homograft, however, was intact. The other patient died nearly 2 years after insertion of the abdominal graft because of rupture of a thoracic aneurysm.

The 2 patients who died after severe gastrointestinal bleeding probably illustrate an interesting complication of abdominal aortic surgery. One died 4 months after insertion of a teflon graft during readmission to the hospital. His clinical history and course strongly suggested erosion of the proximal aortic suture line into the retroperitoneal duodenum. This patient died of a very massive gastrointestinal hemorrhage before he could be moved to the operating room. No autopsy was permitted and therefore we cannot be certain of the cause of death, but the hemorrhage was so rapid as almost certainly to have been due to rupture of the aorta into the gastrointestinal tract. The other patient died in a distant hospital 3 years after insertion of a homograft. She

had undergone a gastrectomy for unidentified upper gastrointestinal bleeding but died of continued bleeding in the postoperative period. It seems entirely possible that this, too, represented another instance of rupture of the suture line into the duodenum.

Hemorrhage into the intestinal tract following aortic surgery has been reported by Sheranian and Boyd and their associates and would seem to be a definite, if uncommon, complication of this type of surgery. Contrary to what might be expected the rate of bleeding, at the onset, may be slow rather than massive and if correctly diagnosed reoperation may be successfully carried out. We believe it is of considerable importance to interpose tissue between the retroperitoneal duodenum and the graft at the original procedure because of this possible late complication.

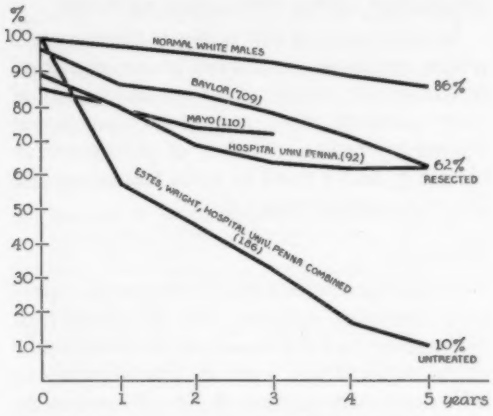


FIG. 2. Comparative survival rates for 3 series of patients with abdominal aortic aneurysms subjected to resection, the combined data from 3 series of untreated aneurysms, and a group of normal white males of comparable age. The resected series are those of the Mayo Clinic, Baylor University, and the University of Pennsylvania. The untreated series includes the data compiled by Estes, Wright, and the University of Pennsylvania. The normal curve was drawn from the actuarial tables of the Metropolitan Life Insurance Company.

### RUPTURED ANEURYSMS

In this series there were 26 patients whose aneurysms had ruptured preoperatively and in whom surgery was undertaken as an emergency measure. The mortality in this group was unfortunately extremely high—85 per cent; only 4 patients survived to leave the hospital. The majority of these 26 patients were in critical condition preoperatively and many had been in shock for prolonged periods. There were several, however, whom we thought would survive the operation, but who died in the postoperative period. The cause of death in these 22 cases was: hemorrhage in 12, coronary occlusion in 4, pulmonary embolism in 2, cerebrovascular accident in 1, pneumonia in 1, infarction of the small bowel in 1, and infarction of the sigmoid colon in 1. More than half the patients died from hemorrhage either during the procedure or within a few days of the operation because of renal shutdown secondary to prolonged hypotension. In the remaining patients various misfortunes attended them during the postoperative period and several of them appeared to be doing well when a sudden fatal coronary occlusion or pulmonary embolus occurred. In 2 patients necrosis of the bowel developed due to interruption of the inferior mesenteric artery, a complication we have not had in the group with unruptured aneurysms although this complication has been reported by Bernatz and Smith and Szilagyi. At autopsy 1 of these patients had severe stenosis of the superior mesenteric artery and had apparently received most of the blood supply to the small bowel via the inferior mesenteric which was ligated at the time of surgery. In retrospect this patient had symptoms of superior mesenteric artery stenosis for many years prior to rupture of the aneurysm but the diagnosis had not been made preoperatively and the condition was not recognized at the time of operation. The surgeon did note, however, that the inferior mesenteric artery was unusually large. The other patient had necrosis of the sigmoid colon.

We are hopeful that with early referral for operative treatment the mortality in this group of patients can be materially improved.

ANEURYSMS ABOVE THE RENAL ARTERIES

In this group of 121 patients there were 3 whose aneurysm extended above the level of the renal arteries. Unfortunately, all of these patients died, one of cardiac arrest during operation, another of postoperative bleeding, and a third of renal failure on the fifteenth postoperative day.

DISCUSSION

In any procedure which carries an operative mortality of 10 per cent, it is important to examine the follow-up data carefully in order to ascertain whether the increase in life expectancy among the survivors has in fact justified the initial risk. Figure 2 graphically presents the combined survival data from 3 series of untreated patients with abdominal aortic aneurysm, 3 series of patients with abdominal aneurysm subjected to excisional therapy, and a curve representing the normal life expectancy of white males of the same age as the mean in our treated series. The series of untreated aneurysms total 186 cases and are represented by the combined data from the studies of Estes, of Wright and associates, and of our own series. The curves representing the operative series are those from this hospital, from the Mayo Clinic—110 cases of Sheranian and associates, and from Baylor University—709 cases of DeBakey and Crawford. From the untreated series it is apparent that only a small percentage of patients survive 5 years if the condition is allowed to follow its natural course. Approximately two-thirds of the deaths among untreated patients were due to rupture of the aneurysm; and a majority of the remaining third died from some form of vascular disease. The Mayo Clinic series and the Baylor University series contain a small percentage of ruptured aneurysms in the follow-up study. However, we excluded those cases in computing their starting point or operative mortality. All operative series start below 100 per cent by an amount equal to the operative mortality which, of course, represents the immediate loss. In these 3 series the operative mortality ranges from 5 to 14 per cent.

Very early in the first year all curves for the treated group cross those of the untreated series, and the advantage of the operative treatment becomes more apparent in the later years. At 5 years, 62 per cent of the Baylor University and University of Pennsylvania series were still alive as compared to 10 per cent of the untreated patients. The uppermost curve on the figure represents the survival rate of normal white males at age 61 years and is computed from the actuarial statistics of the Metropolitan Life Insurance Company. It is interesting to note that the survival rate of patients who survive the operation is somewhat lower than that of the normal male population of a comparable age. This fact undoubtedly reflects the presence of generalized underlying vascular disease and the fact that the operation can prevent only two-thirds of the expected deaths, i.e., those from rupture of the aneurysm. Patients having abdominal aneurysms are not otherwise in average good health.

We believe that resection and grafting of unruptured abdominal aneurysms located below the renal arteries has proved to be the treatment of choice at the present time. This operation should be carried out in all patients who are able to withstand the procedure as soon after the diagnosis as practical. The prognosis of patients who are untreated is extremely bleak. If rupture is allowed, the mortality without operation is essentially 100 per cent and with operation the mortality is still very high. If unruptured the operative mortality in this disease is significant but not prohibitively high and almost certainly will be lowered as further experience is gained. If the patient survives surgery, his expectation of living 5 years is increased many fold.

Although we no longer use homografts we have not seen as high a complication rate from their use as has been reported by others. Sheranian and associates reported 42 per cent of their patients who died after

insertion of homografts did so as a result of failure of the graft. In this series 60 patients had homografts, and of these 27 have now died. Three deaths were definitely attributable to the homograft and 2 additional deaths may have been related to failure of the graft. This means that 11 per cent and possibly as many as 18.5 per cent of the deaths in our series have been due to graft failure. With the use of prosthetic grafts this portion of the mortality should be avoided in future work.

SUMMARY

Prior to 1 June 1960 there have been 121 patients with abdominal aortic aneurysms in whom resection of the lesion was attempted or carried out in the Hospital of the University of Pennsylvania. Ninety-two of these aneurysms were unruptured and located below the renal arteries. The operative mortality in this group was 11 per cent and the 5 year survival rate was 62 per cent. When compared to the 5 year survival rate for untreated abdominal aneurysms of 10 per cent, the value of aortic resection and grafting is clearly established. Any patient having such a lesion should be subjected to surgery if he has a reasonable chance of surviving the operation. It is reasonable to anticipate further reduction in the operative mortality with time.

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# THE HAZARD OF IATROGENIC PNEUMOTHORAX IN CERTAIN DIAGNOSTIC AND THERAPEUTIC PROCEDURES

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THE FACT THAT PNEUMOTHORAX can be very dangerous has been known since the time of Celsus, who made the following statement when discussing the problems of studying anatomy by dissecting living criminals, a practice which was in vogue in Alexandria three centuries before Christ; "It is indeed true that the abdomen, with which our argument is less concerned, can be opened while a man yet lives, but as soon as the knife reaches the thorax, and cuts the transverse septum, which is a membrane dividing the superior parts from the inferior and called the diaphragma by the Greeks, the man at once gives up the ghost and thus it is the breast and its viscera of a dead and not a living man which the murderous physician examines. He has thus performed a cruel murder and has not learned what the viscera of a living man are like." Graham clarified the pathophysiology of open pneumothorax in 1924. Closed pneumothorax in the postoperative patient has not generally been clarified and until relatively recently has not been well understood.

Two hundred and twenty-six cases of pneumothorax occurring in patients treated at the Henry Ford Hospital during the period 1955 to 1959 were reviewed. Seventy-six cases were iatrogenically produced (Tables I and II).

This study was undertaken to review the causes of postoperative and postdiagnostic pneumothorax and to emphasize that certain newer diagnostic and therapeutic procedures are occasionally complicated by authentically proved pneumothorax. These newer techniques are used by general surgeons, thoracic surgeons, neurosurgeons, otolaryngologists, internists, gastroenterologists, and anesthesiologists, and hence they should all be alert for the hazard of pneumothorax. We are deliberately omitting a discussion of pneumomediastinum and pneumothorax following thoracic surgery procedures, since in these instances it is already accepted, recognized, and treated as a consequence of such surgery.

The increasing popularity of these newer procedures, diagnostic and therapeutic, demands that everyone be cognizant not only of the incidence and mechanism of iatrogenic pneumothorax but, equally important, of the ease of recognition and the urgency of immediate and adequate treatment. The diagnosis and treatment of pneumothorax are commonly known and well documented in most surgical texts and will merely be reviewed briefly.

An attempt has been made to clarify and summarize mechanisms and examples by which air may be iatrogenically introduced into the pleural cavity.

## MECHANISMS OF PRODUCTION

There are at least 3 well recognized mechanisms by which air may be iatrogenically introduced directly or indirectly into the pleural cavity to produce pneumothorax.

*Mechanism 1. The inadvertent introduction of air into pleural cavity.* Air may be inadvertently introduced directly into the pleural cavity, as, for example, in the performance of a thoracentesis (Fig. 1). The pneumothorax so produced is usually small and of little significance.

Air may also be introduced inadvertently directly into the pleural cavity if, in draining the pleural cavity, there is a departure from the strictly closed system (Fig. 1). In

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effect, a sucking wound of the chest is produced as well as the development of a tension pneumothorax with its disastrous consequences. Suffice it to say that pneumothorax so produced should never occur.

*Mechanism 2. Puncture of the pleura.* Simple puncture wounds of the parietal pleura without damage to the underlying lung seldom give rise to pneumothorax; the rent in the pleura usually readily seals itself off.

If there is damage to the underlying lung, with each inspiration air is forced out through the injured alveoli into the pleural cavity and a tension pneumothorax is produced (Fig. 2).

This leads to a consideration of the pleural reflections and of the places where inadvertent entrance into the pleura is most likely to occur, with or without damage to the underlying lung. The dots in Figure 3 are intended to illustrate the sites at which the pleural reflections assume greatest clinical importance. The value of a sound knowledge of pleural reflections in avoidance of pneumothorax cannot be overemphasized. A description of the areas of pleural reflection of urgent interest to the surgeon follows.

Cervical pleura: cupula of the pleura.—Does the apex or cupula of the pleura rise above the level of the first rib? The answers "yes" and "no" are alike incorrect. The cupula rises to, but not above the level of the inferior border of the neck of the first rib; but because of the great obliquity of the first costal arch, there is a drop of from 1 to 1½ inches between the vertebral and the sternal ends. It follows that the pleura rises 1 to 1½ inches above the anterior extremity of the first rib. Here the clavicle offers some protection (Fig. 4).

Injury to the cupula and underlying lung may occur during stellate block anesthesia, brachial block anesthesia, subclavian angiography, and in surgery of the lower neck region, e.g., scalene node biopsy, tracheotomy, block dissection, and thyroidectomy. Ditzler reported 5 proved cases of pneumothorax in 526 brachial plexus blocks. He

TABLE I.—PNEUMOTHORAX DURING THE PERIOD FROM 1955 TO 1959

| | *Spontaneous* | *True traumatic* | *Iatrogenic* |
|---|---|---|---|
| 1955 | 18 | 6 | 3 |
| 1956 | 22 | 4 | 7 |
| 1957 | 19 | 5 | 8 |
| 1958 | 35 | 10 | 26 |
| 1959 | 26 | 5 | 32 |
| Totals | 120 | 30 | 76 |

TABLE II.—IATROGENIC PNEUMOTHORAX

| *Procedures* | *No.* | *Pneumothorax* |
|---|---|---|
| Thoracentesis | 255 | 11 |
| Tracheotomy | 165 | 6 |
| Brachial block (supraclavicular) | 767 | 5 |
| Arteriogram (subclavicular) | 36 | 5 |
| Liver needle biopsy | 319 | 3 |
| Radical mastectomy | 307 | 3 |
| Intercostal block | 74 | 2 |
| Stellate ganglion block | 204 | 2 |
| Translumbar aortography | 1389 | 2 |
| Bronchoscopy | 425 | 1 |
| Radical neck operation | 123 | 1 |
| Thyroidectomy | 703 | 1 |
| Parathyroid surgery | 16 | 1 |
| Paravertebral cardiac catheterization. | 287 | 33 |

now uses the axillary route to block the nerves to the upper extremity. Iglauer, who was the first to mention pneumothorax as a complication of tracheotomy in 1915, regarded a lesion of the cupula of the pleura as the cause. His patient recovered. Neffson, in 1943, reviewed 126 cases of tracheostomy and found 17 instances of pneumothorax, 13.5 per cent. In his report, the mortality rate for unilateral pneumothorax was 20 per cent. Bilateral pneumothorax was accompanied by a mortality rate of 90 per cent. However, it is believed now that, in the majority of cases, the mechanism of production is due to opening of the pretracheal fascia and not to injury of the cupula. Knighton has changed his technique and now uses the brachial instead of the subclavian artery in obtaining cerebral angiograms. The complication of pneumothorax is less frequent.

Sternal reflection: costomediastinal recess.—At the level of the fourth costal cartilage, the left parietal pleura usually diverges somewhat from the midline to leave a cardiac recess or notch at the level of the fifth and sixth intercostal spaces. Through this cardiac notch it is sometimes possible to introduce a needle for paracentesis of the peri-

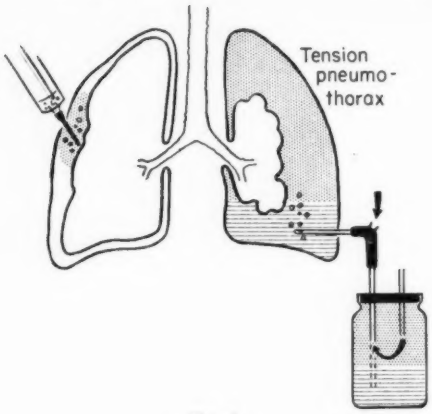


FIG. 1.

FIG. 1. Mechanism 1, air in pleural cavity. Pneumothorax may be caused inadvertently by faulty technique of thoracentesis or by failure of the strictly closed system used in tube thoracotomy.

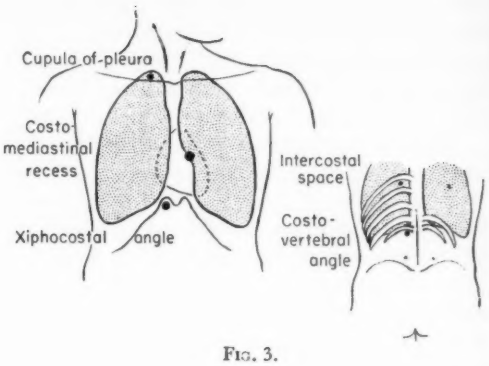


FIG. 3.

FIG. 3. Anatomic areas of pleural reflection of particular importance to the surgeon.

cardium without penetrating the parietal pleura (Fig. 5). It should be noted, however, that this reflection of the left pleura from the midline is not invariable; occasionally, the pleura passes straight downward close to the midline or fails to swing out far enough to extend beyond the lateral wall of the sternum.

Sick, according to Woodbourne, had pointed out the variations in the sternal reflections of the pleura in 1885. Woodbourne has more recently studied the anatomy of the costomediastinal recess (Fig. 5). The solid line in the left precordial region represents the mean found in Woodbourne's series; the broken lines represent variants between which were 70 per cent of the cases in his series.

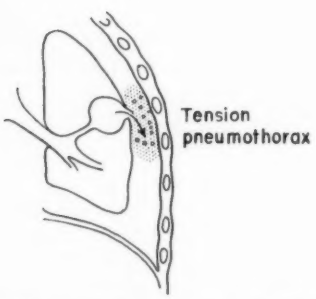


FIG. 2. Mechanism 2, puncture of pleura with and without lung damage. Damage to the pleura and underlying lung may result in a tension pneumothorax, a shifting of the mediastinum, and a serious impairment of ventilatory capacity.

Because of this variability in the cardiac notch of the left pleura, it follows that an intercostal pericardial paracentesis cannot be made in some individuals without perforating the pleural cavity. From the anatomic standpoint, therefore, it would seem wiser to perform pericardial paracentesis by the transdiaphragmatic or paraxiphosternal routes.

Xiphocostal angle.—In Melnikoff's series, the right pleura anteriorly was found to pass below the costal margin in 34.4 per cent of the cases, whereas the left pleura was never observed to do so. In midline epigastric incisions, the superior limit of the incision should never be carried to the right of the xiphosternum (Fig. 5).

Any intercostal space.—A needle passed forward through any intercostal space, with the exception sometimes of the costomediastinal recess, must of necessity enter the pleural cavity (Fig. 6). The underlying lung may be lacerated and pneumothorax result.

Thus, pneumothorax may complicate surgery of the thoracic wall; this was prob-

ably the mechanism responsible in the 2 cases of our series which followed radical mastectomy. Similarly, pneumothorax may complicate intercostal block anesthesia as well as needle biopsy of the liver or spleen. Also, in the performance of a thoracentesis, the underlying lung may be damaged with the production of a pneumothorax.

More recently, it has been seen relatively frequently after cardiac catheterization via the paravertebral route. However, this complication has not been a serious problem.

Right and left costovertebral reflections.—Close to the vertebral column inferiorly, the parietal pleura commonly extends slightly below the twelfth rib but is usually protected from surgical accidents by the transverse processes and the thickness of the overlying musculature. When, as occasionally happens, the twelfth rib is excessively short or absent, this line of reflection comes to lie below the costal margin after crossing the eleventh rib and is, therefore, in surgical danger, as in approaches to the kidney and adrenal and in translumbar aortography (Fig. 7). Injuries to the pleura are also possible when subdiaphragmatic abscesses are drained. Drake stated that in roentgenographic examination of 287 patients from 1955 to 1959, after paravertebral cardiac catheterization, 33 or 11.5 per cent were found to have some degree of pneumothorax. None of these was serious and none required thoracostomy tube drainage.

*Mechanism 3. Introduction of air into the mediastinum.* Air, under tension, in the mediastinum may follow at least 3 different pathways. It may rupture the fragile mediastinal pleura producing unilateral pneumothorax, or it may dissect up into the neck, face, axilla, or thoracic wall; or it may follow the aorta and esophagus into the retroperitoneal area (Fig. 8).

Keis, in 1934, collected 7 cases of fatal mediastinal emphysema following thyroidectomy: in 4 bilateral pneumothorax was also present. He inflated the mediastinum of a corpse and produced pneumothorax.

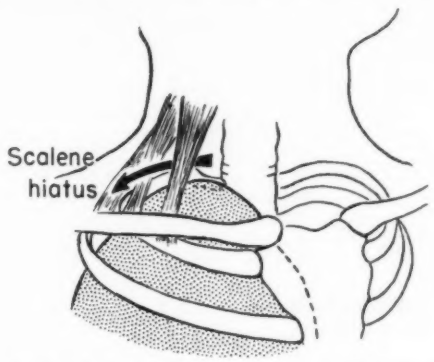


FIG. 4. Mechanism 2, cupula of pleura. The cupula of the pleura may be lacerated in performing a number of diagnostic and therapeutic procedures, such as brachial block, stellate block, and surgery of the lower cervical region including thyroidectomy, tracheotomy, radical neck dissection, scalene node biopsy, and carotid angiography.

Berry, in 1940, repeated the experiments of Keis and demonstrated the same phenomenon. The experiment was repeated by one of us (R. O. A.) in the autopsy room. The process can be watched best by removing part of the lateral chest wall and filling the pleural cavity with water. The air was seen to percolate into the pleural cavity just above the hilum of the lung. The opening of the pleura from the mediastinum is almost certainly valvular, and the pneumothorax so produced is of the tension type.

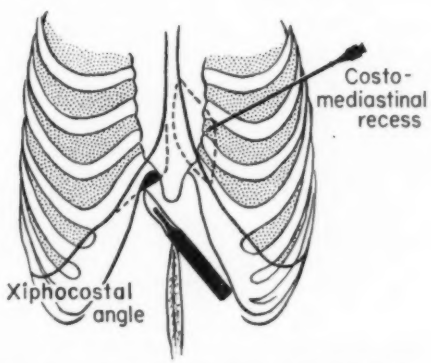


FIG. 5. Mechanism 2, sternocostal reflection. Surgery of the upper portion of abdomen and epigastrium and pericardial aspiration may result in laceration of the pleura at the sternocostal reflection.

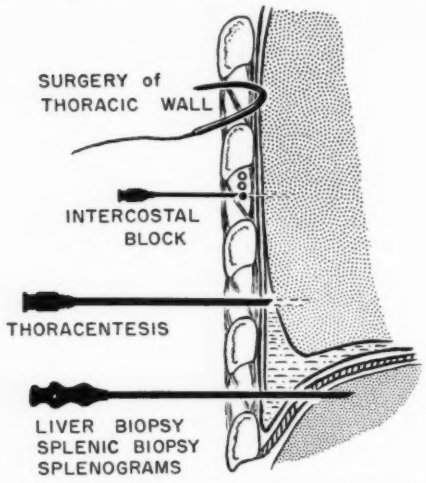


FIG. 6. Mechanism 2, intercostal space. The pleura and/or lung may be injured through any intercostal space by the surgeon's needle, scalpel, aspirating needle, or biopsy needle.

Having established that pneumomediastinum can lead to pneumothorax, we shall now consider the 3 possible mechanisms by which air may be iatrogenically introduced into the mediastinum.

Opening into the pretracheal fascia.—The cervical fascia is comprised of superficial and deep layers. The deep cervical fascia is divided into superficial or infrahyoid, middle or pretracheal, and deep or prevertebral layers. The pretracheal fascia extends inferiorly into the mediastinum where it ultimately blends with the fibrous pericardium (Fig. 9). The prevertebral, or deep layer, is continuous inferiorly with the endothoracic fascia. Between these layers is the perivisceral space enclosing the trachea, esophagus, and thyroid gland. A direct communication exists between this space and the superior mediastinum.

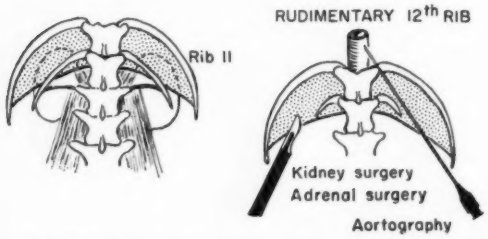


FIG. 7. Mechanism 2, costovertebral reflections. Posteriorly, the costovertebral reflections of the pleura may be damaged in surgery of the kidney, adrenal, aortography, or drainage of subdiaphragmatic abscesses. This is particularly dangerous at the point at which the twelfth rib is rudimentary.

Thus, any surgical procedure of the neck which involves the opening of the pretracheal fascia is fraught with the possible complication of pneumomediastinum and pneumothorax. It is explained not by the fact that the pleura at the apex of the lung is injured, but by the fact that surgical division of the pretracheal fascia permits the free passage of air from the lower neck region into the mediastinum with each inspiratory effort. A partial closure of the superior mediastinal orifice during expiration traps some of the inspired air, with the ultimate production of a tension pneumomediastinum, with the possible development of an ipsilateral, contralateral, or bilateral tension pneumothorax.

It is believed that this mechanism is the most frequent cause of pneumothorax after surgery of the neck. Goldberg and associates reported the occurrence of pneumothorax following tracheotomy. In Forbes' series in 1947, 25 per cent were complicated by pneumomediastinum and 10 per cent by pneumothorax. Ackerman and Bricker, in 1914, discussed the appearance of mediastinal emphysema and pneumothorax after radical neck dissection. Aiken and Smith, in 1950, reported 6 cases of pneumothorax and 2 of pneumomediastinum after block dissections of the neck, 4 of these being fatal, 50 per cent. Bowden, in 1950, and Thomas, in 1957, also reported the complication of pneumothorax after radical neck surgery. Buford, in 1918, and Keis, in 1934, discussed the complication of pneumothorax after thyroidectomy. The latter reported upon 7 cases which were fatal. Seed, in 1949, added 2 more instances of the same complication. Berry, in 1940, reported 4 deaths from tension pneumothorax after thyroidectomy. At necropsy, the cupula was intact in all 4 of the cases reported by Berry.

Damage to respiratory mucosa.—If the trachea is accidentally perforated during surgery of the neck, bronchoscopy, or in endotracheal intubation, air is forced out into the pretracheal space during expiration, and with each inspiration it is sucked into the mediastinum (Fig. 10). In the tracheotomized patient, if the cannula becomes choked or falls out, then during expiration air will be forced out around the sides of the choked cannula, or through the tracheostoma. Pneumomediastinum is likely to develop, particularly, if the neck wound has been sutured too tightly around the tracheotomy tube and air cannot escape to the exterior.

Pulmonary interstitial emphysema produced by rupture of marginal alveoli.—Kelman, in 1919, became interested in the problem of mediastinal emphysema as a result of its development in patients dying of influenzal pneumonia. She observed experimentally that increased pulmonary pressure caused rupture of some of the superficial distended air vesicles and there is escape of air under the visceral pleura.

Macklin and Macklin (17, 18) produced mediastinal emphysema and bilateral pneumothorax by experimental localized overinflation of the lung. They showed that air entering the pulmonary interstitial tissues from rupture of marginal perivascular alveoli dissects its way along the perivascular sheaths to the hilar area, with an eventual escape into the mediastinum (Fig. 11). As this process continues, air accumulates under ever increasing tension which is often relieved by the escape of air into the neck, axilla, retroperitoneal tissues, or into one or both pleural cavities, according to Macklin.

Clinically, this mechanism may be effected by the anesthesiologist who, when using a closed system, exceeds safe intra-alveolar pressures.

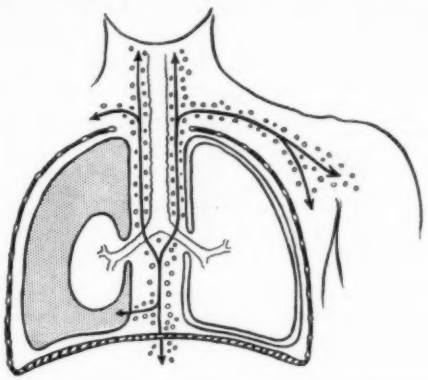

FIG. 8. Mechanism 3. Pneumomediastinum may result in pneumothorax, as shown. Surgery of the neck as well as of the upper or lower mediastinal structures is potentially followed by pneumothorax.

## DIAGNOSIS

Pneumomediastinum and/or pneumothorax can pass undiagnosed because the surgeon may not be conscious of the possibility of this complication. Patients who die from this condition are usually seen by the house surgeon and a confident diagnosis of cardiac failure or shock may be made without the confirmation of a postmortem examination. Careful watching of all patients who have undergone these procedures is mandatory if the high morbidity and mortality rate of this unusual postoperative complication is to be lowered.

Irrespective of its etiology, the diagnosis can be established in the majority of cases by the recognition of a few characteristic signs and symptoms. An awareness that the

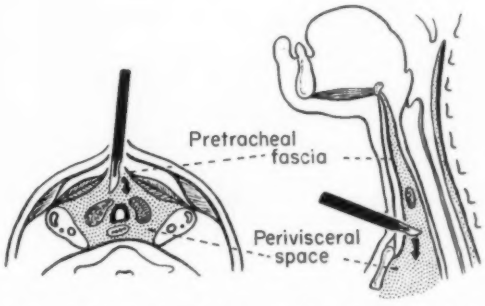


FIG. 9. Mechanism 3, pretracheal fascia. Surgical violation of the pretracheal fascia, associated with tracheotomy, radical neck dissection, thyroid surgery, stellate ganglionectomy, scalene node biopsy, and parathyroid gland surgery may result in ipsilateral, contralateral, or bilateral pneumothorax.

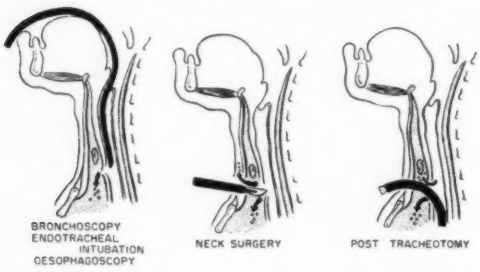


FIG. 10. Mechanism 3, respiratory mucosa damage. The mucosa lining the respiratory tract may be damaged from within or without, as shown. These possibilities are not commonly considered.

possibility of pneumothorax exists in such situations is of prime importance.

Probably the most reliable sign in the immediate postoperative period is subcutaneous emphysema, which usually is present over the anterior and lateral chest wall, the axilla, and neck. It may be the first and only indication that air has accumulated in the mediastinum under tension, and it occurs in more than 50 per cent of the patients.

Chest pain may be substernal initially, suggesting myocardial infarction, or it may be more commonly pleuritic and lateral.

The most important of the variations from normal respiratory patterns is the asthmatic type of breathing, with its discrepancy

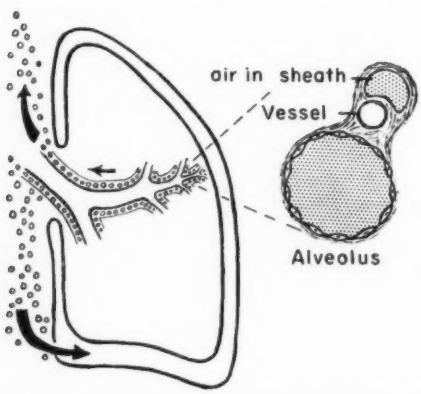


FIG. 11. Mechanism 3, rupture of marginal alveoli into perivascular sheaths. Rupture of marginal alveoli during ventilatory therapy may result in perivascular infiltration of air, ultimately causing unilateral or bilateral pneumothorax.

between the labored respiratory activity of the patient, and the progressively decreasing vital capacity. During the operative procedure in spite of the labored respiratory efforts, the anesthetist will note the minimal movement of the breathing bag. In addition, increased assistance to respiration by manual pressure on the breathing bag is usually required to effect adequate expansion of the lungs.

As the collection of intrapleural air increases, signs of circulatory impairment which are the consequence of hypoxia make their appearance. These include tachycardia, cardiac arrhythmias, and hypotension. Cyanosis of varying degree occurs, as a result of both respiratory and circulatory embarrassment, and is an indication for immediate needle aspiration or closed thoracotomy.

On palpation there may be evidence of decreased respiratory excursions on the side of the pneumothorax. Hyperresonance may be noted on percussion. Distant breath sounds and heart sounds may be detected by auscultation, and there may be a mediastinal crunch synchronous with systole. This valuable sign was first described by Hamman in 1937 and is regarded as pathognomonic of air around the pericardial sac. However, it is not frequently present.

Once the diagnosis has been considered, immediate confirmation by needle aspiration of both pleural cavities should be performed.

Should there be little change in the vital signs, and if the status of the patient is reasonably satisfactory, it is justifiable to wait for roentgenologic confirmation. However, not only is such an examination time-consuming but also the delay in therapy may be extremely hazardous.

## TREATMENT

Once the diagnosis has been confirmed, the importance of prompt and adequate therapy is apparent.

The removal of air from the pleural cavity is most effectively accomplished by thora-

cotomy and continuous underwater drainage. Simple needle aspiration may be ineffective; recurrence of the pneumothorax may occur, since most of these iatrogenically produced pneumothoraces are of the tension valvular type. Needle aspiration, therefore, requires constant medical supervision and repeated roentgenograms to check for recurrence of the pneumothorax. Tube thoracotomy was carried out in 33 per cent of our patients.

Respiratory obstruction, if any, should be removed. If the patient has not yet reacted, an airway is essential. Tracheal suction may be indicated.

Oxygen should be given nasally or by tent but not by positive pressure mask system. Positive pressure breathing in cyanotic, apneic patients with this complication is definitely contraindicated. While indicated with open pneumothorax in reinflating the collapsed lung, it only magnifies respiratory embarrassment in any case of tension pneumothorax. This fact is particularly true if the precipitating factor is presumably due to rupture of marginal alveoli.

Demerol hydrochloride, rather than morphine, since the latter depresses respirations, is used to alleviate anxiety and for its beneficial effect on shock and pain.

The entry of any free air into the deep tissues of the neck and mediastinum should be prevented insofar as possible. If the pneumothorax complicates surgery of the neck, e.g., after thyroidectomy or radical neck dissection, tube drains should be removed and the wound closed.

After tracheotomy, the wound should not be tightly closed around the tracheotomy tube. If, for any reason, the cannula becomes obstructed during expiration, air would be forced out around the sides of the tube, and not being able to find an exit to the exterior, will be sucked into the mediastinum with inspiration.

SUMMARY

1. The detection of 76 cases of iatrogenic pneumothorax at Henry Ford Hospital between 1955 and 1959 indicates that this complication is not rare. The surgeon and the anesthesiologist should be alert to the possibility of its occurrence in all operations in and around the neck and thoracic cage.

2. The possible mechanisms of production are reviewed.

3. Unexplained respiratory distress or deterioration of cardiovascular dynamics in association with mild respiratory difficulties during the operative procedure, or during the postoperative period, should immediately arouse suspicion of pneumothorax, and immediate steps should be taken to establish the diagnosis and institute therapy.

4. A suspected clinical diagnosis may be confirmed by bilateral thoracentesis since waiting for a roentgenologic diagnosis may be disastrous.

5. Simple aspiration of air from the pleural cavity is frequently adequate as a method of treatment for this complication, since most cases are of the tension type.

6. Prompt treatment by the establishment of continuous underwater drainage is essential to avoid severe morbidity and mortality in patients with disturbed cardiopulmonary function caused by the presence of air in the pleural cavity.

7. There were no deaths in this series of cases.

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# THE VALUE OF THE ELECTROCARDIOGRAM IN THE IMMEDIATE POSTOPERATIVE PERIOD

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CONSIDERABLE INFORMATION is available on the use of the electrocardiogram in the preoperative period and during operation, but there have been comparatively few reports on the value of electrocardiography in the first 24 hours after operation. The recovery room of Memorial Hospital with a yearly census of approximately 5,000 patients presented an excellent opportunity to employ the electrocardiogram as a diagnostic tool. This report covers observations conducted over a 21 month period from October 1958 to July 1960.

## SOURCE OF MATERIAL

Since technical facilities did not permit the routine use of electrocardiography on every patient, the study was limited to patients with the following abnormalities of rate or rhythm: (1) any type of arrhythmia or disorder of conduction, (2) bradycardia—pulse below 60 per minute—and (3) tachycardia—pulse over 120 per minute. Included in a fourth group called "evaluation" were 126 patients, 13 per cent of the entire series, in whom it was believed electrocardiography would be of value even though they could not be classified in the first three categories. This miscellaneous group consisted of patients with known severe cardiac disease, hypotension, or respiratory difficulties as well as those who had been anesthetized by the technique of induced hypotension or who had received over 10 pints of blood during the course of operation.

A 12 lead electrocardiogram was taken of every patient in the recovery room who fell into one of the four categories as soon as possible after detection of the abnormality. Serial electrocardiograms were obtained whenever indicated, and transaminase determinations, serial hematocrit readings, and other chemical studies were employed to confirm the electrocardiographic tracings. The electrocardiographic findings were correlated in every case with the clinical picture.[1]

## RESULTS

Out of a total of approximately 10,000 patients who passed through the recovery room during the 21 months of the study, 1 of every 10, or 1,000 patients, met the qualifications for inclusion in the investigation. The 1,000 cases in the series included patients ranging in age from the first through the ninth decade who had been subjected to all forms of anesthesia and every variety of surgical procedure except cardiovascular and obstetric.

There were 341 patients who displayed an arrhythmia or disorder of conduction in the postoperative period. The types of arrhythmia are enumerated in Table I. Although 25 patients showed no arrhythmia by electrocardiography, this did not preclude the fact that arrhythmia may have been present, since a time interval of varying degree elapsed between the detection of the pulse irregularity and the actual electrocardiography.

The presence of myocardial disease appeared to be a significant predisposing factor to the development of postoperative arrhythmia or conduction defects in patients with no preoperative history of cardiac irregularity. Sixty per cent of the patients in

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[1]The electrocardiograms were read, and consultation with the Department of Cardiology was obtained in all cases in which definitive therapy was necessary or the diagnosis was obscure.

TABLE I.—TYPES OF ARRHYTHMIA AND DISORDER OF CONDUCTION IN 341 PATIENTS

| | *No. of patients* |
|---|---|
| Auricular premature contractions | 38 |
| Nodal and supraventricular premature contractions | 22 |
| Ventricular premature contractions | 80 |
| Wandering pacemaker | 16 |
| Sinus arrest | 1 |
| First degree heart block | 2 |
| Bundle branch block | 16 |
| Complete A-V dissociation | 1 |
| Auricular fibrillation | 17 |
| Electrical alternans | 1 |
| Sinus arrhythmia | 122 |
| No arrhythmia on EKG | 25 |
| Total | 341 |
| Patients with preoperative arrhythmia or conduction abnormality*: | |
| No. | 50 |
| Per cent | 26 |
| Patients with no preoperative arrhythmia or conduction abnormality*: | |
| No. | 144 |
| Per cent | 74 |

*Sinus arrhythmia excluded.

TABLE II.—BRADYCARDIA—PULSE UNDER 60 PER MINUTE IN 398 PATIENTS

| *Factors influencing development* | *Per cent of patients* |
|---|---|
| Site of operation | |
| Breast and perineal operations | 62* |
| Presence of myocardial disease | |
| Patients with preoperative and postoperative bradycardia | 53 |
| Patients with postoperative bradycardia only | 36 |
| Operative and postoperative complications in patients with postoperative bradycardia and postoperative EKG evidence of myocardial disease in the absence of known pre-existing cardiac disease | 32 |
| Anesthetic agent | 0 |

115 males, 283 females.
*Series as whole, 47 per cent; series exclusive of bradycardia, 27 per cent.

TABLE III.—TACHYCARDIA—PULSE OVER 120 PER MINUTE—IN 120 PATIENTS

| | *No. of patients* |
|---|---|
| I. Patients with preoperative tachycardia | 31 |
| Adequate medical reason for tachycardia | 25 |
| No apparent cause of tachycardia | 6 |
| II. Patients with no preoperative tachycardia | 89 |
| Cause of postoperative tachycardia in group II | |
| Respiratory complications | 14 |
| Hypovolemia | |
| Total blood volume | 16 |
| Plasma deficiency | 10 |
| Elevated temperature | 2 |
| Severe preoperative myocardial disease | 15 |
| Miscellaneous | 4 |
| No obvious cause | 28 |

TABLE IV.—EVALUATION OF 126 CASES IN WHICH DEFINITIVE CHANGES* IN POSTOPERATIVE ELECTROCARDIOGRAM ARE CORRELATED WITH EXISTENCE OF COMPLICATIONS

| *Reason for postoperative electrocardiogram* | *No. of patients* | *No. of patients with definitive changes* |
|---|---|---|
| Hypotension in operative or postoperative period | 66 | 6 |
| Massive blood replacement | 5 | 1 |
| Induced hypotension during anesthesia | 3 | 3 |
| Respiratory distress during operation or in the postoperative period | 16 | 5 |
| Preoperative severe myocardial disease | 21 | 5 |
| Miscellaneous | 15 | 5 |
| Total | 126 | 25 (20 per cent) |

*Evidence of myocardial ischemia or other abnormality not present in the preoperative period.

whom arrhythmia developed for the first time in the postoperative period had either a history of preoperative myocardial disease, 48 per cent, or had definite postoperative electrocardiographic evidence of myocardial disease in the absence of a clinical history, 12 per cent.

In a recovery room population with a 2 to 1 ratio of female to male patients it is not surprising that there was a large number of cases of bradycardia (398) since the site of operation seemed to be a significant factor in the development of a slow pulse in the immediate postoperative period. Sixty-two per cent of the patients with postoperative bradycardia had operations on the breast or perineum, the operative site being the only point of uniformity in a group with a wide variation in age and physical status. Table II reveals that other factors predisposing to the development of bradycardia in the first few hours after operation were the presence of myocardial disease and operative and postoperative complications involving the respiratory and cardiovascular systems.

The significance of marked tachycardia is shown by the fact that in 72 per cent of all patients with a pulse rate over 120 per minute the rapid rate was directly attributable to the physical condition of the patient prior to operation or to complications occurring during operation or in the immediate

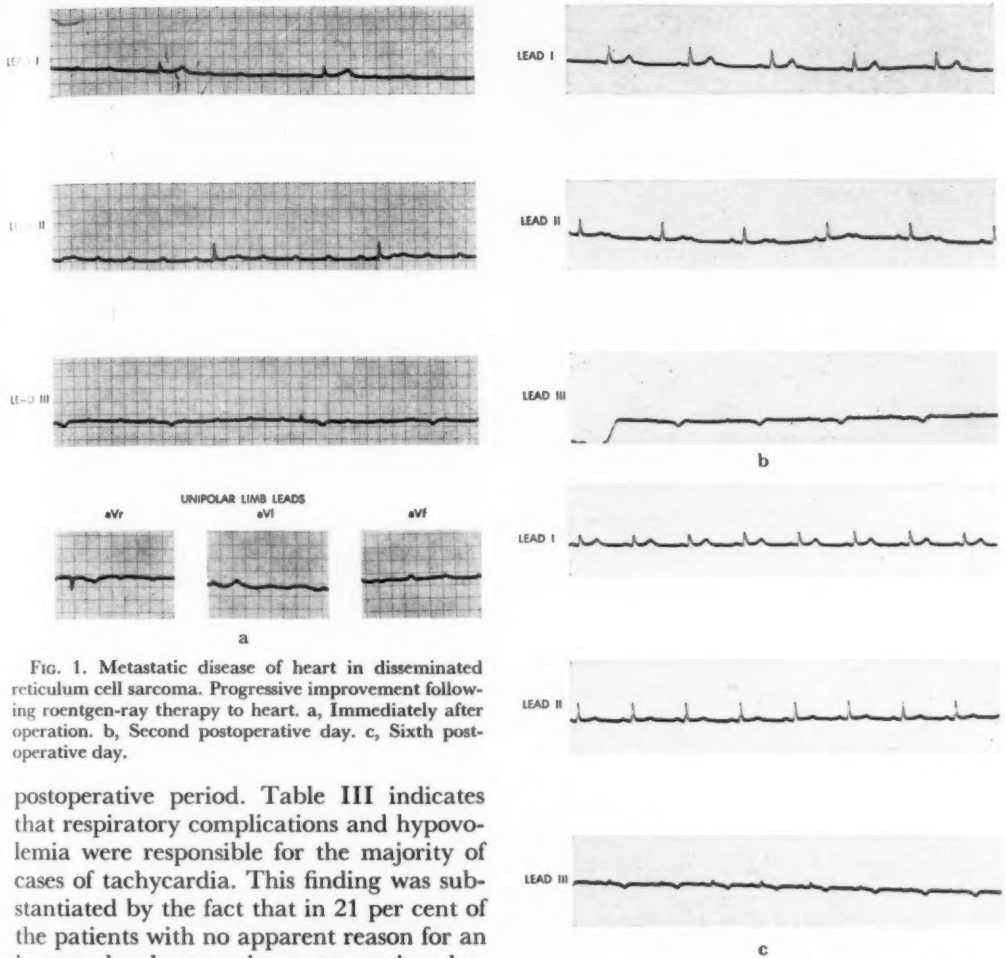


FIG. 1. Metastatic disease of heart in disseminated reticulum cell sarcoma. Progressive improvement following roentgen-ray therapy to heart. a, Immediately after operation. b, Second postoperative day. c, Sixth postoperative day.

postoperative period. Table III indicates that respiratory complications and hypovolemia were responsible for the majority of cases of tachycardia. This finding was substantiated by the fact that in 21 per cent of the patients with no apparent reason for an increased pulse rate the postoperative electrocardiogram was interpreted as showing myocardial ischemia or changes consistent with hypovolemia.

The effect on the electrocardiogram of operative and postoperative complications not included in the three preceding categories is shown in Table IV. In this group, in 25 of the 126 patients evidence of myocardial ischemia or other abnormalities of the electrocardiogram developed which were not present preoperatively.

The electrocardiographic changes which occurred in patients with hypovolemia, due either to a decrease in total blood volume or to a plasma deficiency, followed a fairly definite pattern. In the majority of cases there was depression of the ST segment and lowering or flattening of the T wave, frequently associated with low voltage of the QRS complex. The electrocardiogram reverted to a more normal pattern with restoration of the blood volume. In the massive blood replacement group there was 1 case of ventricular tachycardia.

Changes occurred in the recovery room electrocardiogram of 3 patients anesthetized by the technique of induced hypotensive anesthesia even though the blood pressure

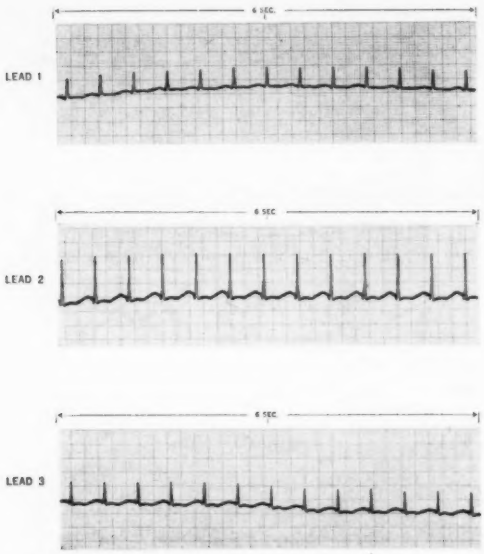


FIG. 2. Metastatic disease of heart in a case of osteogenic sarcoma of femur with extensive metastases.

had returned to a normal level at the time of the recording. Flattening of the T wave in limb and precordial leads occurred in all 3 patients and prolongation of the Q-T interval in 2.

Aside from the general categories which have been discussed, two groups of patients were of special interest and importance. The postoperative electrocardiogram was instrumental in the discovery of 11 cases of acute myocardial infarction and 2 cases of metastatic disease of the heart, unsuspected prior to operation. One of the latter patients was a young man with disseminated reticulum cell sarcoma. Complete A-V dissociation developed during the course of a biopsy of a superficial nodule under thiopental anesthesia. A diagnosis of metastases to the bundle of His was made and roentgen ray therapy to the region of the heart started on the afternoon of the operative day. Therapy was continued for 6 days with complete restoration of normal rhythm. The successive electrocardiographic changes are shown in Figure 1. The second patient was a 16 year old girl with osteogenic sarcoma of the hip in whom a tachycardia of 140 beats per minute developed after catheterization of the femoral artery. An electrocardiogram revealed inversion of the T wave with slight depression of the S-T segment in all limb and precordial leads (Fig. 2). Subsequent electrocardiograms during a prolonged hospital stay were consistently abnormal and the patient finally died with massive pulmonary and pericardial disease.

Table V provides a complete résumé of the 11 cases of myocardial infarction. The original electrocardiographic diagnosis was substantiated by serial tracings and transaminase determinations. Only 5 of the 11 patients had a history of cardiovascular disease and of these 5 only 2 were known to have definite coronary heart disease. The signs and symptoms were atypical in all cases. Tachycardia of sudden onset was the most frequent presenting sign of cardiovascular abnormality, occurring in 5 patients during the course of surgery and in 2 additional patients in the recovery room. Hypovolemia as a possible cause of the tachycardia was not a factor in any of the 7 patients. Other signs of cardiac distress were unexplained hypotension, arrhythmia, bradycardia, and cyanosis. Pain, upper abdominal in character and associated with hypotension, occurred in 1 patient recovering from head and neck surgery. The time interval between the first indication of cardiac abnormality and the electrocardiogram which definitely established the diagnosis of infarction varied from 45 minutes to 14 hours. Two of the 11 patients died in the recovery room, the others made an uneventful recovery. The typical anterior myocardial infarction of Patient 10 is shown in Figure 3.

## DISCUSSION

The fact that coronary occlusion can occur without the typical pain syndrome and, in fact, without any symptom or sign of cardiac difficulty has been reported in the literature on several occasions. Lindberg, Berkson, Stamler, and Poindexter in 1960 reviewed the results of a study conducted

over a 4 year period on 756 nonhospitalized men from 50 to 59 years of age. Three of the 20 cases of definite myocardial infarction that occurred in this group were completely asymptomatic and were diagnosed solely on the basis of routine electrocardiographic tracings. A larger study conducted by Stokes and Dawber on 5,209 patients showed that 21 per cent of 73 myocardial infarctions were of the "silent variety." Johnson and his coworkers in 1959 found that conglomerate and transmural acute infarctions were more frequently recognized before death than patchy or subendocardial lesions. The use of narcotics and the clouded consciousness of the immediately postoperative patient were advanced as reasons for the frequent failure to diagnose acute infarction in the first hours.

Results similar to those in our present study were reported by Driscoll, Hobika, Etsten, and Prager in 1960. In a series of 496 postoperative patients, 12 acute myocardial infarctions were diagnosed by electrocardiogram taken 24 hours after the end of operation. Of these 12 cases, 6 were not suspected clinically and would have been missed except for the electrocardiogram. Contrary to our experience, in which only 5 of the 11 patients had a pre-existing history of cardiovascular disease, all 12 of Driscoll's patients were suffering from either coronary heart disease, hypertension, peripheral vascular disease, or diabetes or had nonspecific abnormal preoperative electrocardiograms. Our results differ from Driscoll's in another respect in that 7 of the 12 patients in her series sustained a significant fall in blood pressure during operation. Except for the sudden appearance of tachycardia in 5 patients and arrhythmia in 1, none of the patients in the present series experienced any cardiovascular or respiratory complications during operation which might predispose to the development of coronary occlusion. The symptoms and signs of infarction in the recovery room were so atypical in every case that the diagnosis would have been delayed or missed entirely without the assistance of the electrocardiogram.

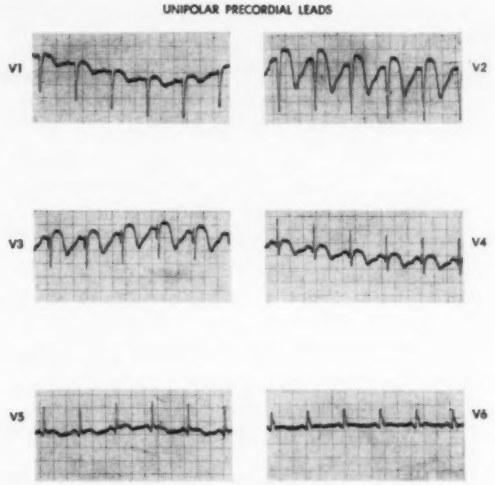


FIG. 3. Anterior myocardial infarction—unipolar precordial leads.

The time interval between the initial indications of cardiac abnormality and the electrocardiographic tracing establishing the diagnosis of myocardial infarction varied from 45 minutes to 14 hours. In the latter cases, however, there was usually a long delay between the onset of myocardial instability and the recording of the electrocardiogram. If an earlier tracing had been obtained in these patients, it is conceivable that the presence of an infarction would have been detected at that time.

Bayley, LaDue, and York showed that temporary occlusion of the anterior descending branch of the left coronary artery in dogs resulted in inversion of the T waves within 3 to 4 seconds and elevation and upward convexity of the S-T segment within 3 to 5 minutes. The latter change was accompanied by upward peaking of the T waves. Although these results obtained in animals are not directly transferable to human patients, our experience seems to indicate that electrocardiographic changes diagnostic of coronary occlusion can occur within a relatively short time after the initial onset of symptoms and signs.

In a previous publication, we (5) have reviewed the pathology, symptomatology, and

TABLE V.—MYOCARDIAL INFARCTIONS

| *Patient Sex Age, yrs.* | *Operation* | *First indication of cardiac abnormality* | *Electrocardiographic findings* |
|---|---|---|---|
| 1 F 47 | Exploratory laparotomy | Tachycardia, 130/min. Onset, 10 mins. after start of operation | 1st EKG—2 hrs. 50 mins. after tachycardia. Sinus tachycardia—inversion T in AVL |
| | | | 2nd EKG—5 hrs. 30 mins. after tachycardia. Myocardial infarction |
| 2 F 39 | Bilateral oophorectomy, liver biopsy | Tachycardia, 140/min. Onset, 30 mins. after start of operation | EKG—55 mins. after tachycardia. Myocardial infarction |
| 3 F 77 | Splenectomy | Tachycardia, 120/min. Onset, 20 mins. after start of operation | EKG—6 hrs. 45 mins. after tachycardia. Subendocardial infarction |
| 4 M 73 | Resection rectosigmoid colon | Tachycardia, 120/min. Onset, 1 hr. 15 mins. after start of operation | EKG—3 hrs. after tachycardia. Anterior septal infarction |
| 5 F 65 | Rt. hemicolectomy | Tachycardia, 120/min. Arrhythmia. Onset, 3 hrs. after start of operation | EKG—3 hrs. after tachycardia. Myocardial ischemia. Patient died before second EKG was taken. |
| 6 M 73 | Construction tube pedicle graft | Hypotension. Onset, 35 mins. after entering recovery room | EKG—45 mins. after hypotension. Anterior infarction |
| 7 M 66 | Excision cancer of back | Bradycardia. Onset, 1 hr. 15 mins. after entering recovery room | EKG—5 mins. after bradycardia. Nonspecific changes |
| | | | EKG—1st postop. day. Subendocardial infarction |
| 8 M 58 | Radical neck dissection and resection of mandible | Hypotension, upper abdominal pain. Onset, operative night | EKG—11 hrs. after symptoms. Subendocardial infarction |
| 9 M 77 | Gastric resection | Tachycardia, 180–200/min. Hypotension. Onset, 2nd postoperative day | EKG—14 hrs. after symptoms. Myocardial infarction |
| 10 F 74 | Exploratory laparotomy | Diaphoresis, tachycardia, 120/min. Onset, 5 to 6 hrs. postop. | EKG—1st postop. day. Anterior myocardial infarction |
| 11 M 62 | Radical neck dissection | Arrhythmia. Onset, 1 hr. 30 mins. after entering recovery room | EKG—45 mins. after arrhythmia. Subendocardial infarction |

electrocardiographic findings in metastatic disease of the heart. Although the diagnosis is made prior to death in only a few isolated instances, the condition is not rare. Metastases to the heart can occur with any type of cancer but are found more frequently in cancer of the lung, breast, malignant melanoma, leukemia, and related diseases. Metastatic disease of the heart should be suspected in any patient with disseminated cancer in whom symptoms, signs, and electrocardiographic findings of myocardial disease develop in the absence of known pre-existing cardiac disease. Since certain forms of cancer are amenable to roentgen ray therapy, the results of such treatment to the heart may be surprisingly successful. The patient with reticulum cell sarcoma in the present series is an excellent illustration of this fact.

Bradycardia and arrhythmia developing in the immediate postoperative period are usually regarded as fairly benign manifestations without much clinical significance. On the contrary, the present study indicates that the occurrence of these abnormalities of rate and rhythm after operation may indicate the presence of previously unsuspected myocardial disease. Tachycardia of any marked degree should also be given serious consideration. In the majority of patients

a pulse above 120 per minute represents a serious medical or physiologic problem which requires prompt therapy.

It is difficult to evaluate the importance of the electrocardiographic findings following induced hypotensive anesthesia on the basis of 3 cases. The tracings were similar to those in hypovolemia and may represent a reduced circulating blood volume in these patients.

Since the average hospital does not have the facilities to perform routine electrocardiography on every postoperative patient, the results of this study indicate that valuable assistance in the early detection of acute myocardial infarction and the differential diagnosis of difficult problems can be obtained by limiting the test to the following: (1) patients in whom a sudden marked tachycardia, with or without hypotension, develops during operation or in the immediate postoperative period, (2) patients with unexplained hypotension not amenable to restoration of circulating fluid volume, (3) patients with marked bradycardia or arrhythmia suggestive of multiple premature ventricular contractions or auricular fibrillation, and (4) those in whom unexplained cyanosis appears in the operating room or the recovery room. In the latter group are included patients who have experienced a period of severe or prolonged anoxia from any cause. Although not all inclusive, adherence to these categories will permit detection of the majority of serious cardiovascular disturbances encountered in the immediate postoperative period.

## SUMMARY AND CONCLUSIONS

1. The postoperative electrocardiogram is essential in the early recognition of coronary occlusion with atypical signs and symptoms.

2. The development of arrhythmia, conduction abnormalities, and bradycardia in the postoperative period should not be disregarded since they may indicate the existence of previously unrecognized myocardial disease.

3. In the majority of cases postoperative tachycardia is a sign of serious abnormality requiring definitive therapy.

4. The electrocardiogram is a valuable aid in the differential diagnosis of postoperative complications of obscure etiology.

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# A STUDY OF BANK BLOOD TOXICITY

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THE ABILITY rapidly to restore or keep pace with major blood loss by transfusion has been an important ingredient in the present accomplishments of surgery. Such massive transfusion has, however, created new problems. Bank blood stored with acid citrate dextrose solution (ACD) is an unphysiologic solution. Its *p*H is below 7, its ionized calcium is virtually zero, its potassium is usually too high, and it is too cold. Usually these abnormalities are rapidly corrected by the body or rendered insignificant by dilution during transfusion but there are many occasions when these mechanisms fail and toxic effects occur. For instance, perfusion of an extremity with essentially pure bank blood as may occur with intra-arterial transfusion is not infrequently followed by tissue death and amputation. Intravenous infusion of large volumes of blood over a short time may have undesirable cardiovascular effects related to the bank blood. This has been cited by Howland and associates (9) as a cause of cardiac arrest and may be one of the causes of so called "irreversible shock" when the bleeding patient ultimately fails to respond to transfusion.

This toxicity of bank blood may be related to the four factors enumerated but their precise roles and relative importance have not been established.

Various attempts have been made to make transfusion blood a less noxious circulatory perfusate and approach the excellence of the transfused blood given by the original method of directly connecting the circulations of donor and recipient.

Most of these efforts have been directed toward modifying the method of preservation. Gibson and his group have reported use of a citrate-phosphate-dextrose buffer which enabled them to reduce slightly the amount of citrate needed to bind the calcium.

Others have attempted to eliminate the need for citrate ion entirely: Smith and associates by employing an EDTA[1] buffer solution, Walters by collecting the blood over ion exchange resins, and Cookson and associates by removing the plasma entirely and substituting a synthetic plasma. Schecter and associates collected and stored blood in the usual fashion but ran it over an ion exchange column just prior to usage.

From the number of proposed methods mentioned, it is evident that no single one has been ideal. When compared to ACD preserved blood, these other techniques have shown either decreased red cell survival time, greater elevation of potassium during storage, or troublesome technical problems during routine collection or administration. Freshly drawn heparinized blood obviates many of these problems and is generally used to prime pump-oxygenator apparatus if the perfusate must be physiologic. However, the short storage time of heparinized blood makes it impractical except for planned procedures and then the required special recruiting of donors is inconvenient.

The present work was undertaken to determine what modifications of ACD blood would be required to render it immediately suitable for maintenance of circulation in its undiluted state. Function of the isolated heart was used as a measure of the perfu-

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Supported by U. S. Public Health Grant H-633(C11).

[1]EDTA is ethylenediaminetetra-acetic acid, also known as versene or versenate.

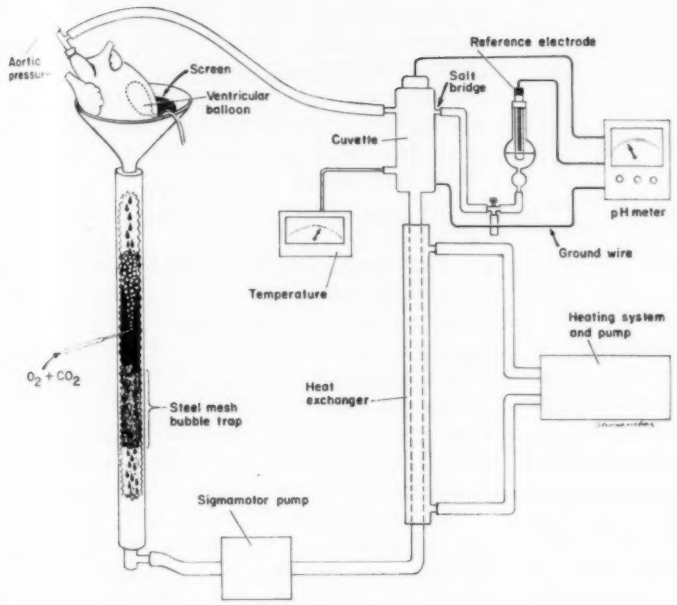


FIG. 1.

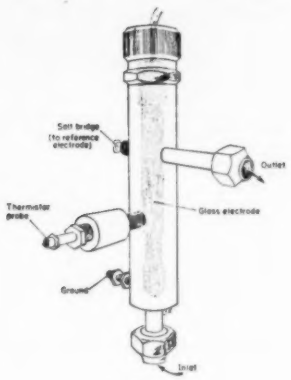


FIG. 2.

FIG. 1. Pump system used.
FIG. 2. Stainless steel *p*H cuvette.

sate's biologic suitability. Principal attention was given to the restoration of physiologic *p*H and ionized calcium levels.

## METHODS

Mongrel dogs weighing between 20 and 30 pounds were anesthetized with the intravenous administration of nembutal, 12 milligrams per pound. A slow intravenous infusion of dextrose and saline was given, and the animal was bled from the inferior vena cava into heparin bags. This blood was used to prime a small bubble oxygenator of the pump system shown in Figure 1. This system consisted of a small sigmamotor pump, a bubble oxygenator and settling chamber, a heat exchanger, and a cuvette for continuous *p*H measurement, as shown in Figure 2. The cuvette contained a glass electrode with a salt bridge to a reference electrode as described by Edmark. A thermistor within the cuvette was used for temperature monitoring. Hydrogen ion concentration was measured on a Beckman zeromatic *p*H meter at 37 degrees C. Blood temperature was kept at 37 degrees C. by the heat exchanger. The total volume of the system was about 300 cubic centimeters.

The heart was removed from the animal before cessation of cardiac action and the aorta was cannulated just distal to the coronary arteries. The isolated heart was then perfused through the coronaries. Blood was allowed to flow from the coronary sinus through a filter and back into the oxygenator. A mixture of 97½ per cent oxygen and 2½ per cent carbon dioxide was used in the oxygenator. Left ventricular pressures were measured by a fluid filled balloon in the ventricle connected to a Sanborn pressure

TABLE I.—EFFECT OF *p*H ON LEFT VENTRICULAR PRESSURES

| Exp. No. | Heparinized blood | | Heparinized blood, ACD and Ca added | | Heparinized blood, ACD and Ca added with THAM | |
|---|---|---|---|---|---|---|
| | *p*H | L.V. pressure | *p*H | L.V. pressure | *p*H | L.V. pressure |
| 1 | 7.4 | 100 | 7.0 | 0 | 7.5 | 75 |
| 2 | 7.3 | 85 | 6.9 | 28 | 7.4 | 172 |
| 3 | 7.4 | 170 | 6.8 | 48 | 7.4 | 156 |
| 4 | 7.2 | 100 | 6.8 | 15 | 7.2 | 120 |
| 5 | 7.3 | 120 | 7.0 | 0 | 7.4 | 85 |
| 6 | 7.2 | 110 | 6.8 | 22 | 7.3 | 150 |
| 7 | 7.45 | 100 | 6.95 | 0 | 7.5 | 150 |
| 8 | 7.35 | 120 | 6.85 | 0 | 7.5 | 130 |
| 9 | 7.3 | 80 | 6.9 | 0 | 7.35 | 150 |
| 10 | 7.4 | 120 | 7.1 | 75 | 7.5 | 100 |
| 11 | 7.4 | 150 | 6.9 | 32 | 7.4 | 160 |

transducer and recorder. Aortic perfusion pressures were also measured.

Initially each heart was perfused with the freshly drawn heparinized blood until cardiac activity was stabilized and baseline observations were made. Ventricular fibrillation which occurred occasionally with the beginning of perfusion was easily controlled with electrical defibrillation, and did not recur. ACD solution was then added in measured quantities to make the blood equivalent to freshly drawn ACD blood—75 cubic centimeters of NIH solution A[2] per 500 cubic centimeters of blood—along with calcium chloride in quantities of .5 grams per 500 cubic centimeters of blood. After stabilization of *p*H and observation of the heart, blood acidity was corrected by adding .2 molar THAM (2 amino- 2 hydroxymethyl 1,3 propanediol) in a volume equal to ACD solution and final observations were made.

The system was then emptied and the procedure repeated with fresh heparinized blood until such time as the preparation deteriorated.

In other animals, after initial stabilization with heparinized blood, this blood was replaced with heparinized blood to which was added: 75 cubic centimeters of ACD solution per 500 cubic centimeters of blood, 0.5 gram of calcium chloride per 500 cubic centimeters of blood, and 75 cubic centimeters of .2 molar THAM per 500 cubic centimeters of blood. The effect of omitting the addition of calcium or of THAM was also studied.

The organic buffer THAM was used to control *p*H after initial studies had shown sodium hydroxide, saline and phosphate or bicarbonate buffer systems to be unsuitable because of the large volumes required if solutions were to be dilute enough to avoid hemolysis during mixing.

## RESULTS

With perfusion of the isolated dog heart with heparinized blood at 37 degrees C. and oxygenation with a mixture of 97½ per cent oxygen and 2½ per cent carbon dioxide, the average *p*H was 7.35. Heart rate, perfusion pressure, and left ventricular pressure were at physiologic levels as shown in Figure 3 and Table I. As ACD solution—75 cubic centimeters of NIH solution A per 500 cubic centimeters of blood—and calcium—as .5 gram of calcium chloride per 500 cubic centimeters of blood—were added, *p*H fell and as it did cardiac rate slowed and the force of left ventricular contractions diminished. As the *p*H reached levels of 7.1, ventricular contractions had decreased to about 50 per cent of their control levels. The hearts appeared dilated. Below 7.0 *p*H effective left ventricular contractions ceased, and cardiac arrest occurred in most cases. In those cases in which some cardiac activity continued at a low *p*H, the left ventricular pressure was at an ineffective level. Cardiac arrest was not a sudden event but occurred only after several minutes of decreasing cardiac activity. This is shown in the second column of Table I and graphically in Figure 3. The critical level for reduction of left ventricular contractions to zero—and thus cardiac output to zero—was between 6.8 and 7.0 in this preparation.

After the *p*H had stabilized at the low level and with the heart arrested in most cases, a .2 molar solution of THAM was added in an equivalent volume to ACD so-

[2]NIH solution refers to the National Institute of Health standardization of acid citrate dextrose solution for preservation of bank blood.

lution. With this the *p*H rose and returned to physiologic levels. As it did, an effective heart beat returned with an initial slow rate which returned to control values. When the *p*H had risen to physiologic levels, the force of ventricular contractions had returned to control levels or higher. If arrest or decreased ventricular contractions were allowed to persist at low *p*H for more than a short period of time, the heart would not return to a control level state in spite of adequate buffering.

With the addition of ACD solution but no calcium, the same sequence of events occurred, i.e., slowing of rate, diminished ventricular contractions and arrest. Addition of THAM without calcium restored the *p*H to normal levels and the heart resumed some feeble activity with low ventricular pressures. If calcium was then added there was prompt return to control levels. Thus both buffer and calcium were necessary in order to preserve adequate function with ACD blood.

Other preparations were perfused with fresh heparinized ACD blood which had been treated by the addition of THAM and calcium chloride in the previously stated quantities. The *p*H of this blood varied between 7.35 and 7.45. With such "restored" blood, heart action was the same as with fresh heparinized blood (Fig. 4).

The amount of calcium chloride necessary to restore the ionized calcium to normal in ACD blood can best be determined by a biologic procedure. With this preparation, titrations were carried out to determine how much calcium was needed to restore ventricular function when the perfusate was ACD blood with *p*H adjusted to 7.4. It was found that .5 gram of calcium chloride or 9 milliequivalents of calcium must be added to 500 cubic centimeters of blood to keep ventricular function at a control level. This observation agrees reasonably well with a value of .6 gram obtained by extrapolation from the Hastings-McLean nomogram for calcium citrate ionization (7, 10).

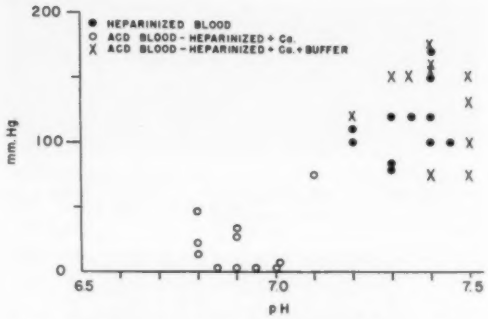


FIG. 3. Chart showing effect of *p*H on left ventricular pressure.

## DISCUSSION

The toxicity of citrate ion per se is not believed by Howland and associates (9) to be clinically important, although it is demonstrable in animals. For inhibition of coagulation, virtual absence of calcium ion is required, so a great excess of citrate is needed. Very rapid massive transfusion can produce sufficient depression of plasma ionized calcium to cause serious cardiac depression. Correction of this defect during massive, rapid transfusions seems dependent on the organism being able both to mobilize calcium quickly for restoration of the serum level and to dispose of the citrate ion rapidly. Thus, while such toxicity is not constantly seen, it may be expected with shock and inadequate peripheral perfusion or with liver disease as shown by Bunker and his group. We have found that .5 gram of calcium chloride or 9 milliequivalents of calcium were needed for each 500 cubic centimeters of blood to restore a reasonable level of ionized calcium in the isolated preparation. It would be presumed that in transfusion, these large amounts would not be necessary because of the occurrence of at least some calcium mobilization and citrate breakdown. Thus Moore has recommended .2 gram of calcium chloride for 500 cubic centimeters of blood for prophylactic treatment of citrate intoxication. For restoration of ACD blood to a suitable state of extracor-

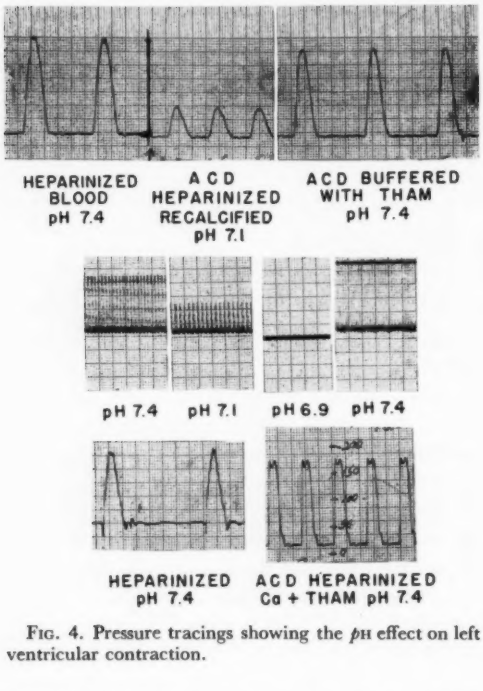
HEPARINIZED BLOOD pH 7.4
A C D HEPARINIZED RECALCIFIED pH 7.1
A C D BUFFERED WITH THAM pH 7.4
pH 7.4
pH 7.1
pH 6.9
pH 7.4
HEPARINIZED pH 7.4
A C D HEPARINIZED Ca + THAM pH 7.4

FIG. 4. Pressure tracings showing the *p*H effect on left ventricular contraction.

poreal circulation, however, the larger amount would seem necessary.

The standard ACD solution used for preserving and storing blood has a *p*H of 4.8 and a unit of blood drawn into such solution has a *p*H of 6.8 to 7.0. During storage, this level goes down further as a result of continued metabolism of red cells, and formations of fixed acids. After 21 days of storage at 7 degrees C, the *p*H has reached levels of 6.6. Thus the transfusion of banked blood is the transfusion of acidotic blood which if given rapidly may lower the intravascular *p*H of the recipient.

Now in the isolated heart, depression of *p*H leads to depression of heart rate and contractility, although this is corrected to a degree by epinephrine release in the intact animal. But in the patient in severe hypovolemic shock a metabolic acidosis tends to develop because of poor tissue perfusion and this may be worsened by epinephrine. Such acidosis will be compounded by poor ventilation in the severely injured. In such patients, massive transfusions of acid blood can aggravate a vicious cycle by pushing blood *p*H down to the point of significant myocardial depression with consequent decrease of output, worsened tissue perfusion, and increased acidosis. Thrower and associates have demonstrated the importance of acidosis in shock, and Nahas and associates found that transfusion of ACD blood buffered with THAM yielded much better survival of shock than transfusion with unbuffered blood.

Rapid infusion of a solution with a high potassium content must be considered. Rapaport has demonstrated that ACD blood in storage shows a progressive rise in plasma potassium to approximately 15 milliequivalents per liter by the twentieth day of storage. The deleterious effect of increasingly high levels of circulating potassium on cardiac function is well known. The high level of serum potassium in banked blood has not been evaluated here. However, there are suggestions that it is not an important factor in the toxicity of banked blood. This may be particularly true if calcium is given, since hypocalcemia exaggerates the effect of hyperkalemia. Bunker and associates in their study of patients receiving massive transfusions, did not find elevations of the serum potassium. Howland and associates (8) in 2 cases of ventricular fibrillation resulting from massive transfusions found the heart blood contained 6.15 and 5.85 milliequivalents of potassium.

Bank blood is stored at temperatures of 5 to 7 degrees C., and rapid administration of large volumes certainly lowers the temperature of the recipient. The depressant effect of hypothermia on the myocardium as noted by Covino and Hegnauer, while of benefit in a controlled situation with extracorporeal circulation is, of course, quite the opposite in the usual surgical procedure. By calculation, 10 cold transfusions would reduce the temperature of a 50 kilogram patient only about 3 degrees C., so significant hypothermia from transfusion would not be usual. Only in an anesthetized patient, unable

to shiver, and losing heat from wound and lungs during a long procedure, would additional cooling from transfusion become significant.

Thus the toxicity of ACD blood when given rapidly and massively seems related primarily to the excess citrate ion present and to the low *p*H. The *p*H can be corrected by the addition of the organic buffer THAM. A .2 to .3 molar solution can be added without hemolysis. A volume of .2 molar THAM equivalent to the volume of ACD solution is required for adequate buffering. The calcium binding effect of the excess citrate ion can be corrected by giving calcium—.2 to .5 gram per 500 cubic centimeters of blood.

While calcium and THAM could be added to blood before transfusion, the required heparinization of the blood would be a disadvantage in the presence of hemorrhage. When these agents are indicated in massive transfusion for hemorrhage, it would seem best to infuse calcium and THAM simultaneously but to avoid its being mixed with the blood.

Initial recalcification and buffering of ACD blood would be desirable in intra-arterial transfusion or perfusion. Extracorporeal pump oxygenator circuits could probably be primed with unmodified ACD blood with the expectation that the heart would rapidly but temporarily fail with the inauguration of perfusion, requiring total circulatory support from the apparatus until natural mechanisms could readjust the *p*H and ionized calcium.

Forte and his associates have demonstrated that such a readjustment of the *p*H will occur after a few minutes if recalcified but unbuffered ACD blood is used for pump oxygenator prime. If it could be done simply, it would seem best not to expose the body to either unphysiologic *p*H or ionized calcium levels. This would seem particularly true in an organ or an extremity perfusion in which the usually accompanying homeostatic mechanisms might be lacking in the circuit.

SUMMARY

The depressant effect of ACD blood on the isolated dog heart has been shown. This depressant effect is evidenced by a decrease in rate and a negative inotropic effect with final cardiac standstill. This has been shown to be due to a lowering of *p*H. An initial effect is seen at *p*H 7.1 to 7.2 with standstill occurring at *p*H 6.8 to 7.0. Calcium alone will not correct this. Buffering of the blood with THAM to a normal range will result in improvement and, in the presence of a normal calcium level, will restore normal cardiac function.

It is suggested that the occasional toxicity of ACD blood when given rapidly and massively is due to hypocalcemia and cardiac acidosis. This may be especially true in hypovolemic shock where there is also metabolic acidosis. One of the lesions of so called "irreversible shock" in the human may be a cycle of increasing metabolic acidosis and diminishing cardiac output which will be aggravated by the administration of an acid transfusion. In this case, and in the case of pump oxygenator primed with ACD blood, initial restoration of *p*H and ionized calcium may be of value.

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# THE ROLE OF REFLEX SPASM IN THE PATHOGENESIS OF VENOUS ISCHEMIA

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PHLEGMASIA CERULEA DOLENS (massive thrombophlebitis, or blue phlebitis) is a rare condition in which ischemia and even gangrene occur in the course of a purely venous occlusion in an extremity. This ischemia is commonly attributed in part to the widespread mechanical occlusion of the veins and in part to a reflex arterial spasm consequent on the irritation produced by the thrombophlebitis. This conception of the etiology of the ischemia has led to some form of spasmolysis being widely advocated as the treatment of choice.

A critical appraisal of the literature, however, fails to confirm any value for these methods, and it therefore seemed desirable to re-examine the premise that reflex arterial spasm plays a part in this disease. The concept of arterial spasm as a major factor in the physiopathology of thrombophlebitis was introduced by Leriche to explain the inability of himself and colleagues (5, 7) to reproduce the features of the chronic postphlebitic syndrome experimentally by extensive venous and lymphatic interruption. In retrospect, it is apparent that these investigators did not appreciate the paradox that it is not the transient venous hypertension associated with venous occlusion but rather the long-continued hypertension of recanalization with incompetence that is responsible for this symptom complex. It seemed, therefore, that this concept of reflex spasm was erroneous and led to a misinterpretation of the clinical evidence. Further support rests mainly on the experimental work of DeBakey, Burch, and Oschner who, using pulse volume as an index of blood flow, reported that ligation of the femoral vein in the dog reduced flow in the limb by 50 per cent, while irritation of the lumen of the vein with sodium salicylate—40 per cent concentrate—produced a further reduction in flow of 25 per cent, provided the sympathetic supply to the limb was intact.

In a preliminary investigation, in which DeBakey's experiments on the rabbit were repeated, it was not possible to confirm entirely his findings (Table I). In these experiments ligation of the common femoral vein, when separated from the effects of the trauma involved in freeing the vessels, was without any significant effect on the pulse volume. In common with DeBakey, however, a profound depression of pulse volume was noted in association with the attempt to introduce salicylate into the lumen of the vein. In view of the great sensitivity of the pulse volume to the effects of traumatic spasm, it seemed equally plausible to ascribe this effect to the trauma of the manipulations and the spillage of the irritant around the femoral artery.

Such evidence justified a more detailed inquiry into the role of reflex arterial spasm in phlegmasia cerulea dolens. Pulse volume was discarded as a measure of flow, first, because of its differential sensitivity to traumatic arterial spasm and, second, because it is affected by changes in venous pressure. A method based on the measurement of skin temperature was selected and an experimental investigation was planned along the following lines: (1) the assessment of the effect on limb blood flow of ligature of the femoral vein and chemical irritation of the vein and surrounding structures; (2) the design of a method of reproducing the pathology of phlegmasia cerulea dolens; and

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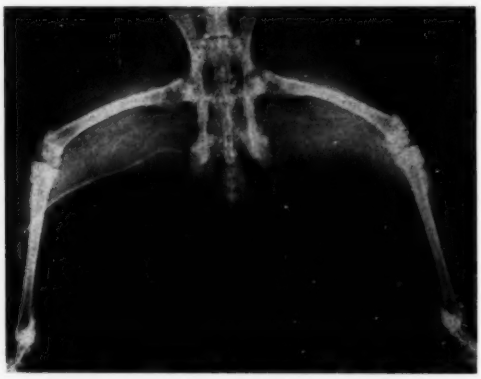

FIG. 1. Aortogram. The right hind-limb is blue. Note venous filling demonstrated on the left.

the measurement of blood flow in such experimental "blue" legs; (3) observation of the effect of total denervation on the blood flow in the experimental "blue" leg.

METHODS

Common brown rabbits varying in weight from 1.7 to 2.2 kilograms were chosen and anesthetized with 40 milligrams of diallylbarbituric acid per kilogram and 160 milligrams of urethane per kilogram body weight administered by intraperitoneal injection.

The method of measuring blood flow was fully described by Burton (1, 2) and involves the calculation of what he terms the "thermal circulation index." This index is based upon skin temperature, but it also takes into account deep body temperature and the temperature of the environment. It is so calculated that, provided the limb circulation remains constant, the index remains unaltered even in a changing environmental temperature. The index is based on a physical analysis of the flow of heat from the body to the environment. This heat flow is envisaged as occurring down two gradients, the physiologic—from the body core to the skin—and the physical—from the skin to the environment.

The flow down these gradients can be expressed as:

(a) $H^1 = C^1(T_c - T_s)$
(b) $H = C(T_s - T_e)$
when H = heat flow (cals./cm.²/sec.)
$T_c$ = core temperature
$T_s$ = skin temperature
$T_e$ = environmental temperature
C = thermal conductivity of the environment
$C^1$ = thermal conductivity of the tissues

The thermal conductivity of the tissues depends on many factors including the proportion of fat and water in the tissues, the thickness of the skin, and the length of the pathway from tissues at the core temperature to the skin. However, the only factor governing $C^1$ which will alter during the course of an experiment is blood flow. The measurement of $C^1$ will therefore provide an index of volume flow and is the closest we can come, by observation of skin temperature, to a direct measurement of peripheral blood flow.

Now in the steady state, the amount of heat reaching the skin must clearly equal that leaving it. In other words $H^1 = H$. Eliminating H we are left with:

$$\frac{C^1}{C} = \frac{T_s - T_e}{T_c - T_s} = r \text{ (the thermal circulation index).}$$

Under experimental conditions, the physical factor C can be kept reasonably constant. Changes in the value of the index will then reflect changes in the conductivity of the tissues; i.e., they will be indicative of changes in the peripheral circulation. The absolute level of the index has no quantitative meaning, but a change in the index, say by a factor of two, means that flow must have increased at least by that factor, i.e., at least twice.

These experiments were carried out in a room where the environmental temperature could be maintained constant within ±0.5 degrees C. This temperature was measured by a mercury thermometer graduated in 0.1 degrees C. and recorded every 2 minutes. Skin and esophageal temperatures were measured with a thermistor equipped with appropriate probes. The working range of this instrument is 20 to 40 degrees C, and the accuracy obtainable is ±0.2 degrees C.

The systemic blood pressure was monitored by means of a cannula in the carotid artery, converted with a P 23 A.C. pressure transducer and recorded on a Model 5 polygraph.

*Part 1.* The temperatures of the skin of both hind limbs of both surgical and control animals, of the esophagus, and of the environment were recorded every 2 minutes; and from this information the "thermal circulation index" for each limb was calculated. The effects of the following maneuvers on the thermal circulation index were separately observed for a minimum of 30 minutes: (a) a gentle dissection in the groin sufficient to free the common femoral vein over a length of 2 centimeters; (b) the insertion of a polythene cannula into the vein and its ligature above and below; (c) the injection of 1 milliliter of 40 per cent weight to volume sodium salicylate into the lumen of the vein via the cannula; (d) the topical application of 1 milliliter of sodium salicylate to the structures that had been exposed in the groin.

*Part 2.* A method of producing selective and almost total occlusion of the venous system of the hind limb was developed. After cannulation of the femoral vein, a tourniquet was applied proximally in the groin. A solution of topical thrombin, 500 units in 5 milliliters of normal saline, was injected retrogradely down the femoral vein. Simultaneously the remainder of the circulation was flooded with 500 units of heparin via an ear vein. The tourniquet remained in place for 5 minutes to allow fixation of the thrombin by clot and was then removed.

Every limb treated in this manner suffered a serious interference with venous return, as shown by the massive edema which developed within 12 hours. About 60 per cent of these limbs showed the classical color change associated with phlegmasia cerulea dolens and were classified as "blue." The remaining 40 per cent showed no color change and corresponded to the more common "white" leg.

TABLE I.—EFFECT OF VARIOUS MANEUVERS ON PULSE VOLUME

| *Maneuvers* | *No. of experiments* | *Mean per cent change in pulse volume* | *Range* | *Significance p* |
|---|---|---|---|---|
| Vessel dissection | 6 | −49 | −16 to −80 | <0.02 |
| Ligature of femoral vein | 8 | −5 | 0 to −16 | 0.05 to 0.10 |
| I.V. salicylate | 5 | −57 | −25 to −80 | <0.01 |

The selective nature of the block, i.e., that it involved the venous system only, was demonstrated in the following ways: (a) Postmortem examination of the limb was performed on most of the animals. Every vein visible in the limb was invariably occluded by clot, but the arteries were anatomically normal. (b) In some animals the limb was dissected during life. Again, every visible vein was occluded. Free bleeding occurred, however, from several arteries, and fresh capillary oozing from divided muscles. (c) In 20 of these animals aortography was performed. Arterial filling, though slower than in the control limb, was always demonstrated in the blue limb. Venous filling, however, was never seen in the treated limb, even in late films, although it was always readily demonstrated in the control limb (Fig. 1).

The thermal circulation index was observed both before and after treatment in 4 blue and 4 white limbs. In these experiments an identical procedure was carried out on the control limb, except that the injection of thrombin was replaced with one of normal saline.

*Part 3.* In this series of 8 animals blue legs were produced as previously detailed, and the thermal circulation index was observed in both the blue and the corresponding control limbs for 30 minutes. At the end of this time, virtually complete sympathetic denervation of both limbs was obtained by severing the femoral and sciatic nerves; and the effect of this maneuver on the thermal circulation index was observed. Finally, the mean perfusion pressure to both limbs was raised 30 millimeters of mercury by a carot-

TABLE II.—THE EFFECT OF VARIOUS MANEUVERS ON THE THERMAL CIRCULATION INDEX (T.C.I.)

| *Maneuvers* | *No. of experiments* | *Mean per cent change T.C.I.* | *Range* | *Significance p* |
|---|---|---|---|---|
| Vessel dissection | 11 | +4 | −20 to +59 | >0.60 |
| Ligature of femoral vein | 12 | +14 | −8 to +100 | >0.10 |
| I.V. salicylate | 6 | 0 | — | — |
| Topical salicylate | 6 | +70 | +33 to +75 | 0.02 to 0.01 |

id infusion of 6 per cent dextran, and this was followed by a further period of observation.

## RESULTS

*Part 1* (*Table II*). Dissection around the vessels in the groin usually had no effect on blood flow. Occasional exceptions were encountered in the direction both of a decrease attributed to extensive traumatic arterial spasm resulting from an inept dissection and of an increase possibly in part due to the warmth of the operator's hands and in part to division of branches of the femoral nerve crossing anterior to the vessels. Statistical evaluation confirms that the mean increase of 4 per cent does not constitute a significant departure from the zero level.

In 7 out of 12 experiments ligature of the common femoral vein did not affect blood flow. In the remaining 5 again variations were encountered in both directions. The mean increase of 14 per cent is not a significant alteration from the resting level.

The careful intraluminal administration of the chemical irritant was absolutely without effect, but the deliberate spillage of the irritant provoked in every case a considerable and very significant increase in the thermal circulation index.

*Part 2.* In 4 limbs which had been treated with thrombin, but which had failed to develop the blue discoloration, no significant alteration in blood flow could be detected. The mean thermal circulation index averaged 90 per cent of that in the control limbs with a range of 70 to 100 per cent. By contrast, in the 4 blue legs a serious degree of ischemia was immediately apparent. Within 60 minutes of treatment the thermal circulation index was on the average only 40 per cent of that in the control limb with a range of 30 to 58 per cent. This difference is statistically very significant ($p = 0.01$ to 0.001).

*Part 3* (*Fig. 2*). In response to denervation in 8 normal limbs the abolition of vasomotor tone regularly resulted in a marked increase in flow, averaging almost 100 per cent with a range of 9 to 250 per cent. In marked contrast, in 8 blue legs there was either no change—in 5 cases—or an increase, markedly less than in the corresponding control limb—in 3 cases. The mean per cent increase was 13 ranging from 0 to 50. The difference between the response in the control and blue limbs is statistically highly significant ($p < 0.001$).

In both the 7 controls and the 7 blue limbs, an increase in perfusion pressure produced a significant increase in blood flow. The increase in the blue limb, however, was always smaller and slower to develop than that in the control limb. The respective mean increases were 71 and 181 per cent, and the difference between them is significant ($p = 0.02$ to 0.05).

## DISCUSSION

*Part 1.* Whether pulse volume or the thermal circulation index is measured, ligature of the femoral vein has no appreciable effect on blood flow in the ipsilateral leg. This result is not surprising when we recall the abundant collateral venous circulation at the root of the thigh, so beautifully demonstrated by Fontaine and Souza-Pereira. It seems unlikely that the results reported by DeBakey and others represent a species difference, and they may be attributable to a failure to differentiate the effect of the tie from the effect of the trauma of tying. The differential effect of such trauma on the pulse volume records—depression of 50 per cent—and on the thermal circulation index—no effect—suggests that the mechanism involved is local traumatic arterial

spasm for reasons which will be discussed shortly.

The failure of intraluminal irritation to in any way affect flow confirms the results of Lynn and Simeone who distended a femoral vein segment with a variety of irritants and failed to demonstrate any effect on pulse volume. Further, Moore and Moore could not provoke pain by the chemical irritation of larger vessels, and this conception is supported from an anatomic viewpoint by the work of Woollard who reported that large vessels are devoid of an afferent nerve supply.

The differential effect on pulse volume and on the thermal circulation index of spillage of a chemical irritant—topical application—to the structures in the groin is very interesting.

Whelan noted that, while needling the brachial artery in man occasionally abolishes the pulse tracing, subsequent venous occlusion plethysmography shows blood flow to be virtually unaltered. Edholm, Howarth, and Sharpey-Schaffer report that in arteriosclerotic limbs, the pulse oscillations are always greatly reduced but that blood flow need not be seriously diminished. This work serves to confirm the opinion of Kinmonth that a localized traumatic arterial spasm need not appreciably interfere with blood flow in the vessel's territory of supply.

It is well known that traumatic spasm is easily provoked in the rabbit femoral artery, and indeed this reaction was appreciable to the naked eye in response both to dissection and to the topical application of salicylate. Thus, the most reasonable explanation of the differential effect of these maneuvers on pulse volume and on the thermal circulation index would seem to be in the differential effect of traumatic arterial spasm on pulse volume and on blood flow.

Our results, therefore, serve to confirm the opinions referred to and constitute a serious indictment of pulse volume as an index of flow. This is one of the major reasons for the selection of a different index of blood flow and is the justification for accepting an increase in flow as the real effect of the spillage of salicylate in the groin.

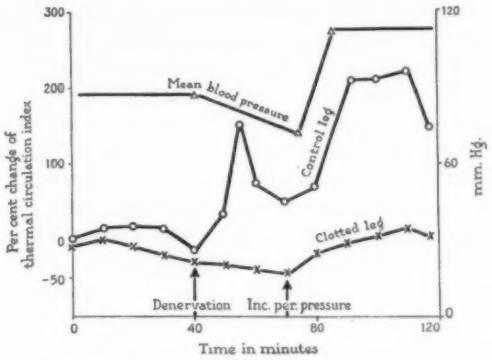


FIG. 2. Graphic reproduction of the results of an individual experiment from part 3.

It is interesting to speculate on the mechanism of the increase in the thermal circulation index in response to chemical irritation.

The possibilities appear to be as follows: (a) Absorption into the general circulation and transference thence to the tissue cells. The salicylate ion is a powerful metabolic stimulant at the cellular level and would doubtless cause a temperature rise if absorbed in this way. The fact that the effect is confined to the ipsilateral leg excludes this explanation. (b) Absorption into the femoral artery, and thence selectively into the tissues of the ipsilateral leg. Prima facie, this seems unlikely, and is made more so by the fact that the same effect, less only in degree, can be obtained with a saturated saline solution, which is not a metabolic stimulant. (c) Local paralysis of the tone of the femoral artery. In view of its well documented effect on pulse volume, this explanation is obviously invalid. (d) A true reflex inhibition of vascular tone. It has been well known for many years that stimulation of a peripheral nerve in physiologic intensities produces such a reflex inhibition of vasomotor tone in the extremity concerned.

In direct contradistinction to the prevailing view then, the results of this investigation suggest that irritation of extravenous structures, comparable to that which may

be caused by the inflammatory reaction of a thrombophlebitis, is more likely to give rise to a vasodilation than a vasoconstriction.

*Part 2.* Evidence has already been adduced that, within the limits imposed by an experimental investigation, the pathologic condition provoked in the experimental blue legs parallels quite closely that of spontaneously occurring phlegmasia cerulea dolens. Two points of difference are, however, apparent. The first is that the occluding agent in these experiments is pure clot caused by a physicochemical reaction between the excess thrombin added and the fibrinogen of the blood plasma. It therefore differs in constitution from a true thrombus. It is, however, apparent from the histologic studies made in the spontaneous disease, that the initiating thrombus is of comparatively minor extent, and that it is the widespread, sudden propagation of clotting from this thrombus that determines the disease picture. In this respect, then, the difference is not great. Secondly, in these limbs organization of the clot has not begun and there is, therefore, no element of "thrombophlebitis." However, "thrombophlebitis" so-called, is not a necessary basis for the production of the spontaneous disease, for cases have been reported of an obvious primary clot and no evidence of any inflammatory reaction. Furthermore, it has been shown that the addition of such an irritative process is more likely to increase than to decrease flow.

In these limbs, which have all suffered a serious degree of venous interruption, there must be a fine dividing line between the white, in which the circulation remains adequate, and the blue, which suffer a serious ischemia. The fact that both sets of limbs have suffered a similar disease suggests that the dividing line lies in the degree of completeness of the mechanical block.

*Part 3.* The fact that the increase in flow in response to denervation is very much smaller in the blue limb than in the control would seem to offer conclusive proof that in this preparation, at least, reflex vasomotor spasm plays no part in the production of the ischemia. If spasm were a factor, then denervation could be expected to allow an increase in flow greater on the affected side than in the control limb. The fact that a much lesser increase was observed not only rules out the possibility of spasm but further suggests that some purely mechanical factor is preventing even the normal rise associated with the abolition of vasomotor tone. Presumably, this factor is the absence of a sufficient cross-section of patent venous bed to support any increase in the circulation.

The response of blood flow to an increase in perfusion pressure is interesting in two respects. Firstly, it serves to underline the grave local consequences of hypotension in this condition and, by contrast, the considerable local improvement that can be effected by restoring an adequate blood pressure. Secondly, it allows us to speculate on the nature of the peripheral resistance in these limbs. In the otherwise normal but denervated limb an increase in perfusion pressure has its expected result. The peripheral resistance is flaccid, the vessels passively dilate, and a considerable increase in flow is achieved. In the blue limb, by marked contrast, the increase in flow is much less. This can only be interpreted as indicating that the peripheral resistance is no longer responsive to reflex control but is mechanically fixed. It seems reasonable to assume that it no longer resides in the arterioles, but is now situated in the venous side of the circulation, and is dependent on the mechanical blockage of these channels by clot.

## CONCLUSIONS

If the general parallelism between the experimental blue leg and spontaneous phlegmasia cerulea dolens is accepted, and it would seem reasonable to do so at least in those cases without phlebitis, then this conclusive demonstration of the absence of significant reflex spasm becomes very meaningful. Furthermore, these results indicate that the addition to this pathologic condi-

tion of a process resembling inflammatory irritation would not be expected to cause reflex spasm.

It seems most reasonable then to attribute the ischemia occurring in phlegmasia cerulea dolens entirely to the mechanical effects of widespread venous occlusion. This explanation envisages the venous circulation so embarrassed by massive thrombosis that it is unable to support a flow sufficient to maintain the viability of the tissues in its drainage area. It is clear that if blood cannot leave a given circulation, then no new blood can enter it. The blood continues to pulse at a normal pressure in the arterial system, but capillary circulation is restricted to replacing that volume of blood to which the venous system can still give exit, plus the volume of fluid which leaves the capillaries to give rise to edema. In addition, this extravagant edema which develops very rapidly no doubt further disturbs the minute circulation by small vessel compression.

This is not the place to discuss the treatment of the spontaneous disease, except to say that the results of this investigation support the impression gathered from the literature that spasmolytic treatment, in particular lumbar sympathetic block, has no useful part to play. The choice lies between the conservative regimen described and used with success by Veal, Duggan, Jamison, and Bauersfeld and thrombectomy advocated by Ossius.

SUMMARY

A critical review of the published cases fails to confirm any useful effect from spasmolytic measures in the treatment of phlegmasia cerulea dolens.

The theory of reflex arterial spasm on which such treatment is based was postulated on incorrect premises.

The results of an experimental investigation are presented:

1. Ligature of the femoral vein does not affect blood flow in the limb.

2. Chemical irritation of the structures in the groin, simulating the inflammatory irritation of thrombophlebitis, causes a reflex increase in blood flow rather than the reverse.

3. A method of producing massive venous occlusion in the rabbit hindlimb is described. Such limbs reproduce the pathologic and clinical features of phlegmasia cerulea dolens and suffer a serious degree of ischemia.

4. Evidence is presented that in the production of this ischemia reflex arterial spasm plays no part.

It is concluded that the ischemia seen in the spontaneous disease should be attributed solely to the mechanical effects of massive venous occlusion. There is no theoretic reason to assume that spasmolytic therapy would be of any value.

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# THE TREATMENT OF CEREBRAL ANEURYSMS BY LIGATION OF THE COMMON CAROTID ARTERY

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THERE IS CONTROVERSY concerning intracranial surgical intervention versus ligation of the carotid vessels in the neck in the treatment of cerebral aneurysms.

Although some surgeons believe that for most aneurysms intracranial attack, preferably under hypothermia, offers the best chance for cure and lessened morbidity, there is accumulating evidence that good results can be obtained in aneurysms situated adjacent to or below the bifurcation of the internal carotid by ligation of the internal or common carotid artery in the neck.

There is also controversy as to which artery to ligate. Although ligation of the internal carotid produces a greater decrease in intra-arterial pressure distal to the ligation than does ligation of the common carotid, the neurologic complications following ligation of the former are said to be more frequent than after ligation of the latter.

Dorrance as early as 1934 gave the arguments for common carotid ligation, and his masterly presentation is still pertinent now.

Bakay and Sweet found that, after temporary occlusion of the common carotid artery in patients with brain tumors, the percentage of fall in systolic pressure is essentially the same in all intracranial branches of the artery as it is in the neck immediately distal to the site of closure.

The proponents for internal carotid ligation believe that the intra-arterial pressure drop following ligation of the common carotid is not maintained because of collateral circulation from the external carotid and circle of Willis.

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However, the one observation by Sweet and associates questions this: "Late studies of intracarotid pressure in 1 case 5 weeks after the original measurements showed that the initial fall in pressure after clipping of the common carotid artery was fully maintained despite the possible increase in collateral blood supply which may have developed intracranially."

Heyman and associates studied the changes in the distal carotid pressure in 24 patients with vascular lesions after occlusion by a Crutchfield clamp on the common carotid artery. They did this by direct measurements of intracarotid pressure and by ophthalmodynamometric determinations of retinal arterial pressures.

They found that although there is a slight return to normal pressure within a few weeks, a significant reduction in pressure was maintained in the distal carotid system for as long as 6 to 19 months after closure of the clamp.

They also found that after common carotid ligation approximately one-fourth of the residual pressure in the distal internal carotid artery is contributed by the collateral circulation supplied by the ipsilateral external carotid artery. They conclude that occlusion of the common carotid artery is of value in management of aneurysm of the carotid system.

Another point for ligation of the common carotid versus that of the internal carotid is that it is technically easier.

The following data represents our experience with ligation of the common carotid artery employed in the treatment of cerebral aneurysm.

CLINICAL DATA

Forty-one patients with vascular malformations proved by angiography were treated by ligation of the common carotid artery followed in some cases by craniotomy with trapping, clipping, or removal of the lesion. There were 31 berry aneurysms; 7 arteriovenous malformations; and 3 carotid cavernous fistulas.

There were no postoperative deaths or neurologic complications after ligation in the group with malformations or fistulas, and their clinical course will be described in a future presentation.

This report deals with the 31 cases of berry aneurysm. Twenty-five patients were treated by ligation of the common carotid artery and 6 by ligation of the common carotid followed by intracranial clipping or trapping. The patients' ages ranged from 20 to 71 years; 16 were over 50 and 15 were under 50. Twenty-three were female and 8 were male. The patients had the usual symptoms and signs associated with cerebral aneurysms. In 1 case, unilateral tinnitus preceded the rupture of an ipsilateral posterior communicating aneurysm. Twenty-six per cent of the patients had a history of chronic hypertension, whereas 35 per cent had blood pressure elevated above 160 systolic or over 90 diastolic on admission.

Laboratory studies for bleeding tendencies in 16 patients, 53 per cent, were negative. Serologic studies of the blood were positive in 2 of 28 patients tested. In both postligation paralysis developed.

Roentgenograms of the skull showed a linear calcification in the wall of the aneurysm in 5 patients with aneurysms of the cavernous internal carotid. Four of these also showed an erosion of one or many of the following structures: the dorsum sellae, greater wing of the sphenoid, anterior or posterior clinoid process, and lateral wall of the sphenoid sinus. The remaining studies were negative.

Electroencephalograms were made in 7 patients and were of no clinical value.

Cerebral angiography with the usual radiopaque contrast medium in multiple injections of 10 to 20 cubic centimeters into the exposed carotid artery was carried out early in this series. Since the Chamberlain biplane stereoscopic angiographic unit became available, only 2 percutaneous injections of 10 cubic centimeters of 35 per cent hypaque have been necessary for bilateral studies. Eight of the 31 patients had bilateral angiographic studies and all showed unilateral aneurysms. Percutaneous vertebral angiography was negative in the single study in this series.

However, during the past year, retrograde brachial artery angiography has offered a dependable method for visualization of the vertebrobasilar and ipsilateral carotid artery systems.

Twenty-seven patients, 87 per cent, had 1 aneurysm. Four patients, 13 per cent, had 2 on the same side: anterior cerebral and middle cerebral; posterior communicating and internal carotid proximal to the bifurcation; and posterior cerebral and middle cerebral. One patient had 2 aneurysms on the outer third of the middle cerebral artery (Table I).

Five patients had aneurysms of the middle cerebral artery; the aneurysms were quiescent in 3 and the neurologic signs in these patients were produced by rupture of another aneurysm on the same side.

The interval from onset of symptoms to ligation was from 1 to 7 days in 2 patients;

TABLE I.—LOCATION OF ANEURYSMS

| | *Right* | *Left* | *Total* |
|---|---|---|---|
| Posterior communicating | 8 | 5 | 13 |
| Internal carotid, distal to cavernous, proximal to bifurcation | 2 | 3 | 5 |
| Cavernous sinus | 3 | 1 | 4 |
| Bifurcation of internal carotid | 2 | 1 | 3 |
| Anterior cerebral, proximal to anterior communicating | 0 | 2 | 2 |
| Anterior cerebral, distal to anterior communicating | 0 | 0 | 0 |
| Anterior communicating, 1 | — | — | 1 |
| Anterior cerebral and anterior communicating | 1 | 0 | 1 |
| Middle cerebral, 6 | | | |
| Inner third | 1 | 1 | 2 |
| Middle third | 2 | 0 | 2 |
| Outer third | 2 | 0 | 2 |
| Total | 21 | 13 | 35 |

from 8 to 13 days in 7; from 14 to 20 days in 7; from 21 to 28 days in 7; from 35 to 56 days in 4; and there were no data from 4. The shortest interval was 5 days and the longest was 56 days.

The sensorium was observed before ligation. Twenty-one patients were awake, 4 were drowsy, and 6 in stupor or coma. Four of the 5 postoperative deaths were in the latter group. Most investigators agree that the highest mortality follows ligation in the unconscious patient.

The Matas test was not made. However, the carotid artery was temporarily completely ligated, usually under local anesthesia, for 15 to 30 minutes, and if no complications occurred, permanent ligation was carried out.

### OPERATIVE DATA

A local anesthetic was used in 24 patients and sodium pentothal in 7.

The type of ligature used was two 6 millimeter umbilical tapes placed 2 centimeters apart, which completely occluded the common carotid artery in 25 patients. Two tapes were removed promptly after a postligation hemiplegia. One tape was extruded 7 months after ligation. The remaining tapes have been well tolerated for a maximum period of 11 years. A periarterial cellophane wrap with its tapes was completely extruded 3 years after insertion. A stainless steel clip has been in situ for 6 years.

Four Selverstone clamps have been well tolerated up to 6 years, but this small series gave us no evidence of superiority over one stage occlusion by ligature. Mount (14) was not impressed with the value of the Selverstone clamp in a series of 65 cases of cerebral aneurysms including 10 patients treated by gradual occlusion of the common carotid artery, though he states that he may not have followed Selverstone's method.

Mortality and morbidity after ligation were as follows: 25 patients had ligation of the common carotid artery only. Four of these died, 1 at 14 hours; 2 at 24 hours; and 1 at 48 hours because of bleeding.

The neurologic status worsened in 5 patients after ligation, at ½ hour, 1 hour, 4 hours, 12 hours, and 19 days, respectively.

One patient, aged 54, with hypertension had no preligation neurologic deficit. Angiography showed an aneurysm of the anterior cerebral artery near the anterior communicating artery and partial "spasm" or occlusion of the ipsilateral anterior cerebral, middle cerebral, and internal carotid arteries. He was awake during ligation and became hemiplegic ½ hour later. The ligature was removed and marked recovery took place in 9 hours. He worked as a machinist until death from coronary thrombosis 8 years later.

One patient, aged 51, normotensive and with an aneurysm of the posterior communicating artery had a preligation partial ophthalmoplegia. She was awake at ligation, and hemiplegia developed 1 hour later. The ligature was not removed. She is ambulatory with a partial hemiparesis 9 years later.

One hypertensive patient, aged 62, with an aneurysm of the cavernous internal carotid and a third nerve paralysis was awake at ligation. Hemiplegia developed 4 hours later. The ligature was not removed. She is ambulatory with personality changes and hemiparesis 9 years later.

One patient, aged 60, with hypertension had an aneurysm of the postcommunicating artery and carotid siphon, "spasm" of the ipsilateral anterior cerebral artery, and plaques in the internal carotid artery. She was drowsy and hemiparetic on the left side before the common carotid artery was occluded to one-third of its diameter. Aphasia and right hemiparesis occurred 12 hours later. She is unimproved 1 year later.

One patient, aged 38, normotensive but luetic, had an aneurysm of the internal carotid proximal to the bifurcation. She was awake with no neurologic deficit before gradual occlusion was achieved with a Selverstone clamp over a period of 5 days. Aphasia and contralateral hemiplegia developed 14 days after complete occlusion.

She was awake and spinal fluid was clear. The clamp was not released for fear of emboli. The patient is partially aphasic and hemiparetic but does light housework 2 years later.

Six patients had ligation of the common carotid artery followed by prompt intracranial intervention. In 3 there were no postligation complications and the craniotomy was performed to clip or trap the aneurysm. In the remaining 3, craniotomy was performed because of worsening of the neurologic deficit by persistent bleeding. There was 1 postoperative death among these 6 patients. Thus, the postoperative mortality for the 31 patients was 5 deaths, 16 per cent. There were 8 complications, 26 per cent.

### FOLLOW-UP

Six patients who had craniotomy after ligation were excluded from this follow-up survey. The surviving 21 patients of the 25 who had ligation of the common carotid only were followed up to a maximum of 11 years: 2 for 1 year; 6 for 1 to 3 years; 6 for 5 to 7 years; and 7 for 8 to 11 years.

Sixteen patients had no added neurologic deficit after ligation. In many the preligation neurologic deficit improved or cleared. Four of the 16 patients had ophthalmoplegias. Two recovered completely, 1 partially, and 1, unimproved, died suddenly from an unknown cause 1½ years later.

Eight patients had third nerve palsies. Three of these recovered completely after ligation, but 1 died 5 years after ligation in status epilepticus from rupture of the aneurysm into the temporal lobe; 4 made partial recoveries, but 1 of these died 5 years after ligation from rupture of the aneurysm; and 1 could not be located for follow-up study.

Of the remaining four, 1 with third nerve palsy and hemiparesis made a complete recovery and is working full time as a machinist 9 years after ligation. One with unilateral facial numbness died of a rupture of the aneurysm during her fourth attack 2 years after ligation. In 1 patient with no preligation or postligation deficit a weakness of the right lower part of the face developed, but the patient is otherwise well 5 years after ligation. One patient had a partial recovery from aphasia and hemiparesis and is working as a boiler operator 6 years afterward.

Death during the follow-up period occurred in 5 patients. Four died from a rupture of the original aneurysm, confirmed by autopsy in 3. Two died 2 years and 2 died 5 years after ligation. Another patient died from a heart attack after working as a mechanic for 8 years.

Thus, of a total of 25 patients with a berry aneurysm who had ligation only, 9 now are dead, 8 from rupture of original aneurysm.

Three of the 5 immediate postoperative deaths were in hypertensive patients over 50 years of age, whereas only 2 of the 5 who died during the follow-up period were hypertensive; 2 of these 5 were under 50 and 3 were over 50 years of age. One of these died from a coronary attack. The 7 patients who have been followed up for the maximum periods of 8 to 11 years were over 50 years of age at the time of ligation, and 6 of the 7 were normotensive. The 1 death in this group up to the time of this report was from a coronary attack in a hypertensive male aged 62. Thus, ligation of the common carotid artery in normotensive individuals of 50 to 65 years of age with cerebral aneurysm is compatible with many years of survival. However, complications that follow ligation were more frequent in those over 50 years old than in those less than this age.

In 2 of the 21 patients, 10 per cent, postoperative convulsions developed. One had hemiplegia 1 hour after ligation, and aphasia and hemiplegia developed in the other 19 days after ligation. The attacks are controlled by medication.

Progress arteriography was carried out in 5 patients after ligation. Three of these had a craniotomy after ligation. In 1 the progress arteriogram made 13 days after ligation showed no change in size of the posterior communicating aneurysm, and 4 days later the aneurysm was clipped intracranially. In

the second patient, progress arteriography 6 days after ligation showed excellent filling bilaterally except below the bifurcation which was the site of the aneurysm later trapped intracranially.

The third patient with a bleeding aneurysm of the anterior communicating artery and a quiet aneurysm of the right middle cerebral artery was treated by ligation of the common carotid artery and, 5 days later, by clipping of the right anterior cerebral artery. Progress arteriography carried out 7 months and 4 years after craniotomy showed no change in the size of either aneurysm. This patient has a partial foot drop but works full time in a factory.

Progress arteriography was carried out in 2 patients who had ligation only. In 1 with an aneurysm of the internal carotid, angiography 2 years after ligation showed no change in the size of the aneurysm and the patient died shortly thereafter from rupture of the aneurysm. In the other, with an aneurysm of the posterior communicating artery, angiography 11 years later showed a questionable decrease in size. This patient, now 71, is working as a power plant engineer and has frequent headaches.

Thus, in 3 cases of aneurysms of the posterior communicating artery, progress angiography at 13 days, 2 years, and 11 years, respectively, after ligation of the common carotid artery only showed no definite change in the size of the aneurysm.

Hardy and associates carried out progress angiography on 10 of 46 patients after ligation of the common carotid artery. There was cross filling of the anterior cerebral artery in 4 instances but without visualization of an aneurysm. The aneurysm filled in 2 instances, 1 at 11 months after partial ligation and, in the other, 3 years after permanent ligation.

Johnson performed progress angiographic studies in "some cases" after ligation of the common carotid and before ligation of the ipsilateral internal carotid. His studies showed that (1) ligation of the common carotid reduced the size of the aneurysm; and (2) after an interval of 6 weeks or more the flow was from the external to the internal carotid. He concluded that, initially, common carotid ligation is only slightly safer but that eventually internal carotid ligation is more effective.

Mount and Taveras (15) described the results of surgical therapy in 51 patients having intracranial aneurysms as shown by 54 progress arteriograms made from 10 days to 8 years after operation. Included in their data are 11 patients who had ligation of the common carotid and 30 with ligation of the internal carotid in the neck. They conclude that progress arteriography is not a completely definitive method of evaluating results and that the clinical signs and symptoms are important.

In a later paper Mount (14) confirms from postoperative angiograms that, although ligation of the internal carotid artery is more successful than ligation of the common carotid artery in treatment of intracranial aneurysms, ligation of common carotid is followed by fewer complications.

Ophthalmodynamometry was not performed before ligation and was carried out in only 1 patient 10 years after ligation and in another 11 years after ligation. In both, the pressure was lower on the ligated side, although in 1 the angiogram 11 years after the ligation still showed the aneurysm. Perhaps the intra-arterial pressure in this patient was decreased enough to avoid marked distention and rupture.

The studies by Tindall and his associates (10, 25) suggest that ophthalmodynamometric findings after common carotid ligation support the value of such ligations in the treatment of cerebral aneurysms.

## DISCUSSION

Table II shows the mortality and complication percentages obtained from many reports after ligation of either artery.

Davis and associates and Hardy and coworkers, have reported large series with favorable results following ligation of the common carotid artery. However, Dandy

TABLE II.—MORTALITY AND COMPLICATIONS REPORTED BY VARIOUS INVESTIGATORS AFTER LIGATION OF COMMON OR INTERNAL CAROTID IN NECK FOR CEREBRAL SACCULAR ANEURYSMS

| | | *Common carotid* | | | *Internal carotid* | | | |
|---|---|---|---|---|---|---|---|---|
| | *Date* | *No. pat.* | *Per cent complicat.* | *Per cent mortal.* | *No. pat.* | *Per cent complicat.* | *Per cent mortal.* | *Remarks* |
| Schornstein | 1940 | — | — | — | — | — | — | 60 pat.—mixed ligat.—mortality 13 per cent |
| Dandy | 1942 | — | — | — | 88 | 6 | 4.5 | Includ. vascular malform.—some partial ligat. |
| Olivecrona | 1944 | — | — | — | 11 | 18 | 0 | 13 cases vas. malf.—1 com. c. ligat. excluded |
| Falconer | 1951 | 18 | 17 | 17 | 8 | 37 | 12.5 | Common c. were 2 stage ligation |
| Voris | 1951 | — | — | — | 40 | 23 | 17.5 | — |
| Poppen (Poppen and Fager, 1960) | 1951 | — | — | — | 101 | 7 | 4 | Pract. all aneur. arising from I.C.—few c. carotid and clamp ligat. |
| Wechsler, Gross, and Cohen | 1951 | 17 | 6 | 12 | — | — | — | Mainly aneurysms of circle of Willis—1 death foll. ligat. and craniot. |
| Bassett, List, and Lemmen | 1952 | — | — | — | 29 | 45 | 3.4 | Varied aneurysms—2 ligat. com. carotid—3 part. |
| Norlén | 1952 | 21* | 14 | — | 17 | 29 | 6 | — |
| Jefferson | 1952 | — | — | — | — | — | — | 142 pat.—mixed ligat.—mortality 8 per cent |
| Black and German | 1953 | 20 | 10 | 10 | 15 | 0 | 0 | Aneur. cav. I.C.—9, some combined ligat. aneur. cerebral I.C.—26 |
| Hamby | 1954 | — | — | — | — | — | — | 13 ligat. mixed—mortality, 31 per cent |
| Rowe, Grunnagle, Susen, and Davis | 1955 | — | — | — | — | — | — | 28 ligat. mixed—mortality, 10 per cent |
| Davis, Wetzel, and Davis | 1956 | 75 | 4 | 18 | — | — | — | 62 verified by angiography or autopsy. I.C.—21; p.com.—16; A.C.—12; M.C.—8; misc.—5. Few had ligat. I.C. or both |
| Shenkin, Polakoff, and Finneson | 1958 | — | — | — | 19 | 32 | 5 | 2 c. carotid ligat. included |
| Hardy, Thomas, Webster, and Gurdjian | 1958 | 54 | 7 | 5.5 | — | — | — | I.C.—22; M.C.—14; A. com.—7; A.C.—4; P. com.—4; P.C.—3 |
| Mount | 1959 | 10 | — | — | 55 | — | — | All ligat. part. or compl. with Selv. cl.; total mortality, 14 per cent; complications, 17 per cent |
| McKissock, Richardson, and Walsh | 1960 | 37 | 27 | 8 | — | — | — | All aneur. of I.C. at or near post. com. art. control study (see text) |
| Scott and Skwarok | 1960 | 31 | 26 | 16 | — | — | — | Aneur. of circle of Willis (see text) |

*12 were followed by ligat. of int. carotid.

as well as Poppen and Fager (19, 20) have reported large series with good results following ligation of the internal carotid.

An average of the statistics in Table II reveals a 6 per cent mortality after internal carotid ligation as compared with 11 per cent after common carotid ligation. However, complications after internal carotid ligation were twice those after common carotid ligation—22 per cent versus 11 per cent.

The value of these statistics is doubtful because of such preligation factors as location of the aneurysm, blood pressure level, condition of the patient, and state of the collateral circulation.

The answer as to which vessel to ligate might come from the controlled studies by McKissock and his group who have reported favorable results following ligation of the common carotid artery when com-

pared with craniotomy and nonsurgical care for aneurysms of the internal carotid at or near the posterior communicating artery. However, they conclude that "although ligation of the common carotid artery for such aneurysms appears preferable to medical care or craniotomy, we are not entirely satisfied with ligation of this artery because of its high complication rate." They have not as yet reported a like study after ligation of internal carotid artery in the neck.

SUMMARY

1. Thirty-one patients with berry aneurysms proved by angiography had ligation of the common carotid artery. Six of these patients underwent subsequent intracranial surgical intervention.

2. The patients' ages ranged from 20 to 71 years. Sixteen were more than 50 and 15 were less than 50 years of age. There were 23 females and 8 males.

3. The preligation symptoms, signs, roentgenograms, and laboratory findings are evaluated.

4. Twenty-six per cent of the patients had a history of chronic hypertension and 35 per cent had hypertension on admission.

5. Aneurysms with occasional exceptions produced the classical neurologic deficits.

6. No relation could be established between the interval from onset of symptoms to ligation and postoperative mortality or morbidity.

7. Twenty-one patients were awake before ligation, 4 were drowsy, and 6 in stupor or coma. Four of the postoperative deaths were in the latter group.

8. The Matas test was not made; however, the patient was observed for 15 to 30 minutes after ligation, usually under local anesthesia, before the incision was closed.

9. There were 8 complications, 26 per cent, promptly after ligation, 2 after the clamp and 6 after tape ligation.

10. There were 5 postoperative deaths after ligation, 16 per cent. One death followed postligation craniotomy.

11. Twenty-one of the 25 patients who had ligation of the carotid only survived operation and were followed up to a maximum of 11 years. Sixty-two per cent were followed up for 5 to 11 years.

12. Of the 5 patients who had prompt complications after ligation, 1 with hemiparesis made a complete recovery but died of a heart attack 8 years later; 1 is bedridden and aphasic at 1 year; and 3 are ambulatory with an improvement in hemiparesis, 2 at 9 years each and 1 at 2 years after ligation. Thus, there were no follow-up deaths caused by bleeding from the aneurysm in patients whose neurologic deficit developed from the ligation.

13. Sixteen patients had no added neurologic deficit after ligation. The preligation deficit cleared in 6, improved in 6, and did not change in 4. Four of the 16 died from rupture of the aneurysm, 1 at 1½ years, 1 at 2 years, and 2, 5 years after ligation. Thus, there was an additional mortality of 19 per cent from recurrent hemorrhages within 5 years after ligation.

14. Ligation of the common carotid artery in awake normotensive individuals 50 to 65 years old is compatible with many years of survival. Yet, postligation complications are more frequent in this age group.

15. In 10 per cent of patients occasional convulsions developed after ligation of the common carotid artery.

16. Progress arteriography was carried out in 5 patients after ligation. The aneurysm was not visualized in 1, and in 1 it was still present in the anterior communicating artery 4 years after ligation followed by clipping of the anterior cerebral artery. In the remaining 3 patients, all with aneurysms of the posterior communicating artery, angiography 13 days, 2 years, and 11 years, respectively, after ligation of the common carotid showed no change in the size of the aneurysm.

17. Ophthalmodynamometry was not performed before ligation and in only 2 patients after ligation, one 10 years later and the other 11 years later. In both, the pressure was lower on the ligated side, although

in 1 the angiogram 11 years later showed no change in the aneurysm.

## CONCLUSIONS

1. This study suggests that at present one cannot decide on the superiority of ligation of the common carotid artery in the neck over that of the internal carotid for the treatment of cerebral aneurysms.

2. The results following ligation of either vessel in the neck for cerebral aneurysms of the internal carotid and the posterior communicating vessels compare favorably with and are often superior to the results after intracranial intervention for these lesions.

3. The important point seems to be not which vessel to ligate but when not to ligate.

4. Ligation of the common or internal carotid artery in the neck singly or in sequence should not be performed under the following conditions: (a) If the patient cannot tolerate temporary occlusion of the carotid on either side, as shown by the Matas test; (b) low blood pressure; (c) severe hypertension; (d) stupor or coma; (e) if bilateral angiography shows narrowing or "spasm" of arteries distal to the aneurysms on either side or inadequate collateral circulation; or (f) if angiography and clinical evaluation suggest that intracranial intervention offers a better chance for saving life or achieving permanent obliteration of the aneurysm with fewer complications, i.e., supraclinoid position of the aneurysm with adequate neck for clipping; associated intracerebral hematoma; or repeated attacks of bleeding from an accessible arteriovenous malformation.

5. The final consideration must be the condition of each patient, and in some instances ligation of either artery, even in the face of the contraindications listed, might be a life-saving measure.

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# ARTIFICIAL URINARY SPHINCTER

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AN OPERATION to construct an efficient artificial urinary sphincter has intrigued surgeons for many years. Attempts have been made to increase periurethral pressure with slings of fascia lata and rectus sheath. The urethra has been surrounded with striated muscle such as the pyramidalis or gracilis with an intact nerve and blood supply. The bulbocavernosus and ischiocavernosus have been transplanted or plicated, and wedging and tightening the internal urethral orifice have been carried out by Young (13) and, later, Lowsley. In certain types of urinary incontinence some of these operations produce excellent results. The Kelly plication operation for the correction of incontinence resulting from cystourethrocele is very efficient as is the Marshall-Marchetti vesical neck suspension. Conditions which are primarily due to loss of support of the vesical neck and urethra by surrounding tissues lend themselves to correction in this way. Conditions involving anatomic defects in the vesical neck, prostatic urethra or bladder, neurogenic dysfunction, aplasia of the urethra, epispadias, exstrophy, extensive scarring, and contraction of the urethra or vesical neck have not been amenable to predictable surgical cure by any of these methods.

In the last several years there have been some seemingly unrelated lines of investigation which point rather clearly to the principle to be applied in these situations. Roentgenographic and cineroentgenographic studies of the mechanism of urination by Muellner, and by Benjamin and Kjellberg and their associates have shown that resting continence and initiation of micturition are dependent largely upon the internal sphincter or vesical neck. This is smooth muscle. There have also been studies and clinical applications, by Ockerblad, Barnes and Farley, and Dillon, of tubed flaps of detrusor muscle used to bridge gaps in the urinary tract mainly as replacement of damaged ureters. In some of these cases the tubed flaps were found to be capable of resisting the increased intravesical pressure, thus preventing reflux to the affected kidney. In 1953 we attempted to form tubed flap urethras in dogs and in a single patient with a congenital vesicovaginal fistula (12). The tubes were successful; however, continence was not achieved. It remained for Lapides in an elegant and decisive manner to show that urinary continence in dogs was maintained at the internal sphincter by virtue of the resistance it presented to urinary outflow, the resistance varying directly with the inherent tension of the urethral wall and the length of the urethra and inversely with the radius of the urethral lumen (LaPlace's Law). He visualized opening of the internal sphincter as a process of active contraction of the smooth muscle of the detrusor and urethral musculature, shortening the urethra and increasing its lumen. His tubed flap urethras in patients produced continence and allowed voiding.

The principle thus evolved is the opposition of smooth muscle to itself with or without the formation of a neourethra from a tube of detrusor in which the lumen at rest is occluded and of sufficient length to prevent the outflow of urine but in which, with active contraction of the detrusor, the lumen will open and the tube shorten sufficiently to permit urination. The clinical applica-

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This study was supported in part by the Lewis Michelson Research Fund.

tions of this principle are somewhat staggering and include many conditions previously impossible to treat. This is the basis for Young's partially successful repair of a patient with exstrophy of the bladder in 1922 (13). It may be possible to provide operations for replacement of the urethra, postprostatectomy incontinence, and urinary diversion to the abdominal wall in place of a permanent cystotomy.

## EXPERIMENTAL PROCEDURES

In the light of our previous experience in making tubed flap urethras for dogs to serve merely as conduits, we believed that an answer lay in anatomically trying to reproduce a sphincter by narrowing a tubed flap over a short distance. Four female mongrel dogs were then subjected to the following varied procedures and closure of the vesical neck (Fig. 1).

The first dog had a small bladder flap 1.0 by 0.5 centimeter raised on the anterior wall of the bladder and anastomosed to the distal stump of the urethra. The flap urethra was closed snugly around a No. 5 F. ureteral catheter at a single point with one suture. By the twelfth postoperative day the dog was voiding satisfactorily via the urethra. At 1 month an attempt was made to transplant the urethra to the abdominal wall to verify the control of urination as being due solely to the tubed flap sphincter. Urinary extravasation from sloughing of the urethra made it necessary to sacrifice the animal at 5 weeks. The extirpated bladder showed the flap to be intact and patent. There was a stricture at the site of anastomosis. Filling the bladder with saline showed the flap to be responsible for continence. Fluid spurted freely from the tubed flap when the bladder was squeezed.

The second animal had a 1 by 1 centimeter tubed bladder flap raised on the anterior bladder wall and anastomosed to a tubed skin flap from the abdominal wall. A stricture developed in this animal at the anastomotic site between the bladder flap and skin tube, but manometric readings at 3

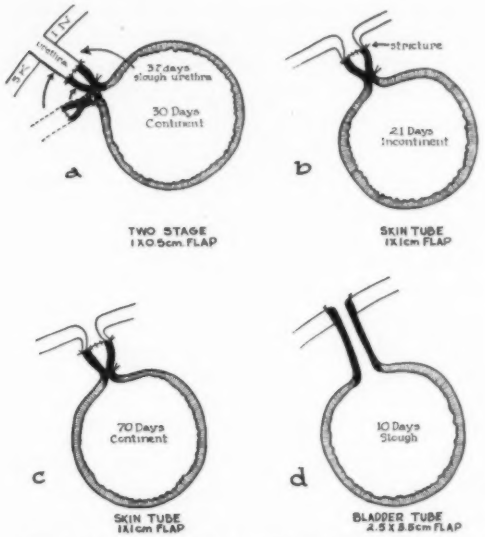


FIG. 1. Diagram of experimental methods attempted in dogs to convert a tubed flap of bladder muscle from a simple conduit into a passively functioning sphincter by plicating it at a single point.

weeks showed resistance by the neosphincter to volumes of 60 cubic centimeters and pressures of 18 centimeters of water.

The third animal had the same procedure, but full continence developed after a short period of urinary leakage. Needle cystograms prior to sacrifice at 10 weeks showed no evidence of leakage, and autopsy specimen showed a soft, distensible flap of bladder musculature at the sphincter site.

The fourth animal had a considerably larger flap raised on the anterior bladder wall, approximately 2.5 by 3.5 centimeters, and this was anastomosed directly to the abdominal wall skin with no attempt made to occlude the lumen at the initial operation. As planned, a second operation was to be performed at 2 weeks and the tube was to be plicated in a single area to create a sphincter. Unfortunately, the blood supply of the tubed flap had been exceeded and the animal died at 10 days of urinary extravasation. Postmortem examination revealed necrosis of the distal half of the flap.

At this point we had tentatively convinced ourselves of a few wild generaliza-

tions with regard to tubed flaps of bladder muscle: (1) They can be relied upon to conduct urine; (2) they are easily distensible if uninvolved by external scarring; and (3) if the lumen is occluded over a relatively short distance, resistance of the smooth muscle in the wall is enough to produce continence.

Two classes of patients suggested themselves as possibilities: patients requiring permanent cystotomy and those with exstrophy of the bladder which we tried to reconstruct along the lines of Sweetser, Powell, and Lattimer and their associates rather than transplant the ureters to the colon.

### APPLICATION TO EXSTROPHY OF THE BLADDER

In this congenital abnormality there is probably an embryologic nonunion of the abdominal wall in the medial plane as a result of failure of the somatopleure to unite. The cloacal membrane perforates, but with an abnormal ventral extension, and there is persistent opening of the blastophore. The pubic symphysis remains separated. The rectus muscles attached laterally leave a V-shaped lower abdominal defect in which lies the everted bladder. The firm, fibrous backing of the bladder is formed by the abnormally extended "symphysis," and the trigone and urethra lie, oddly, on top of the symphysis.

Simple invagination of the exstrophied bladder with closure and reconstruction of the urethra suggests itself immediately upon observing this defect. The difficulties here are several: (1) The apparent amount of bladder varies widely from patient to patient and in some appears quite small. (2) An adequate sphincter must be constructed without producing obstruction. This construction is complicated in males by the rigidity of the cleft prostatic urethra. (3) The abdominal wall must be reconstructed. (4) The role of angulation of the urethra over the symphysis must be assessed. (5) The external genitalia must be reconstructed. (6) The upper urinary tract may be damaged by either reflux or obstruction and aggravated by operation.

These problems are impressive but not insurmountable. The features of the repair which we believe are important include: (1) adequate freeing of the bladder from its underlying fetal fibrous backing; (2) the use of smooth muscle alone in construction of the sphincter; (3) deep undermining of the trigone; (4) minimal suture of the sphincter and avoidance of external compression to allow for distensibility; (5) overocclusion of the sphincter to provide dilatation of the bladder and subsequent hypertrophy and balance; (6) firm abdominal wall reconstruction with fascial flaps, care being taken not to compress the sphincteric area; and, (7) operation during the neonatal period to avoid fixation and shrinkage of the bladder. With these features in mind, we devised the following operation.

### DESCRIPTION OF OPERATION

After routine preparation and draping of the patient in the supine position, the ureteral orifices are identified on the surface of the exstrophied bladder and No. 4 ureteral catheters are passed to the renal pelves bilaterally. An incision is then made through the skin and subcutaneous tissues surrounding the exstrophy in its upper three-quarters (Fig. 2). This incision is deepened into the space of Retzius bilaterally, undermining the bladder wall. The ureters are identified by palpation at this point in the operation, their course is estimated, and care is taken to avoid damaging them. The bladder is then undermined laterally and separated from its peritoneal attachment. The urethra and the vesical neck are partially undermined for approximately one-third of the width of the exstrophied trigone and posterior urethra on each side. After adequate mobilization the bladder is closed by approximating the laterally freed walls with a midline suture of interrupted No. 4-0 chromic gut in the mucosa and a reinforcing layer of No. 4-0 chromic gut suture in the muscularis. A stab wound cystotomy is placed to the right or left of the suture line, to be brought out

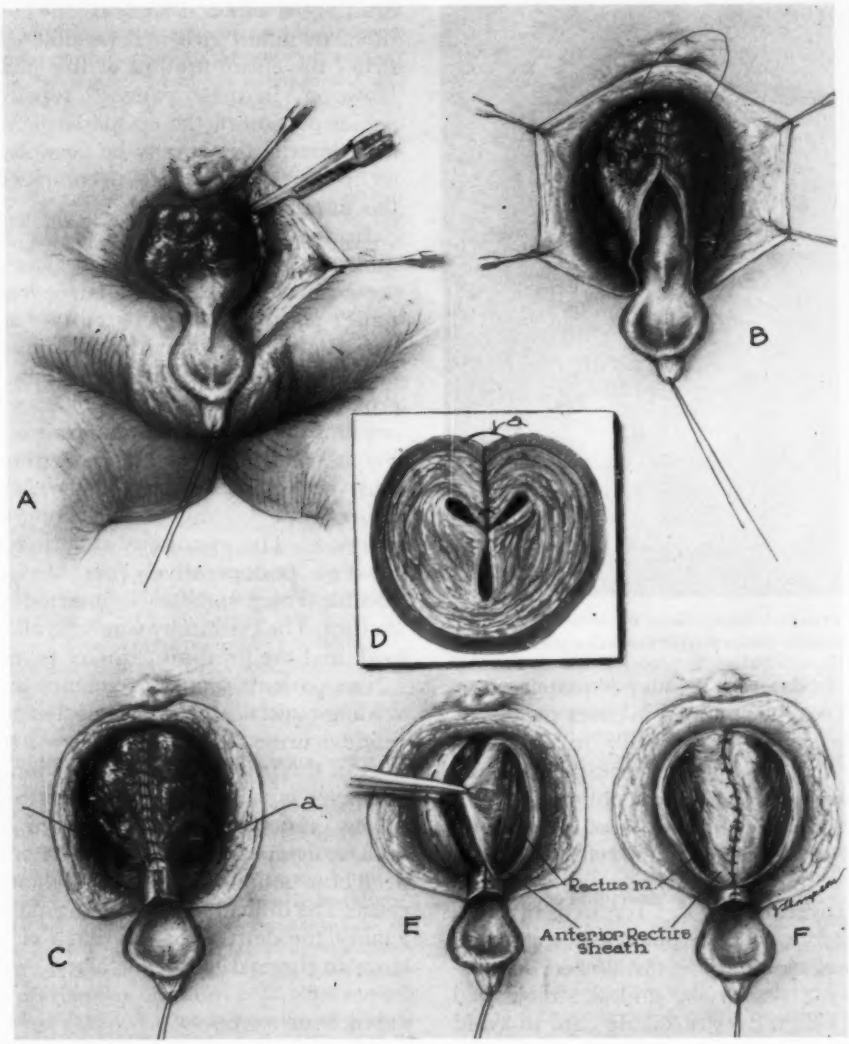


FIG. 2. Drawing showing the steps in reconstruction of the exstrophied bladder. A, Skin incision being carried into the preperitoneal space. B, The bladder is freed from its fascial and peritoneal attachments. The inverting suture has been started. C, Closure of the vesical neck and proximal urethra. The plicating stitch can be seen at the approximate level of the distal trigone. D, Cross section at the level of the neosphincter to show plication and occlusion of the urothelial-lined, smooth muscle tube. E, The development of fascial flaps from rectus sheath for reconstruction of the abdominal wall. F, Fascial flaps sutured over the recessed bladder.

through a separate stab wound in the skin after closure of the abdominal wall. The undermined trigone at the region of the vesical neck which has been closed as a tube is occluded with a simple plication stitch which, in effect, invaginates the dorsal portion of the vesical neck, providing a puckered, neointernal sphincter composed entirely of smooth muscle and lined with urothelium. The rectus fascia and external oblique aponeurosis are then undermined superiorly and, by means of a relaxing Y-V

FIG. 3. Patient 1. Preoperative intravenous pyelogram showing marked bilateral hydroureteronephrosis.

incision in the midline, an adequate amount of fascia can be obtained to cover the defect. Occasionally it is necessary to cut semicircular flaps of anterior rectus sheath and aponeurosis of the external oblique, leaving them attached in the region of the superior margin of the bladder and reflecting them medially and ventrally to form a firm fascial covering for the recessed bladder. The bladder is then placed in the retroperitoneal space above the fibrous connection of the symphysis, and the mobilized fascia is closed over it, taking care to avoid compression of the area of the neosphincter with fascia or, subsequently, with the subcutaneous tissue or skin. The skin of the abdominal wall is then mobilized by undercutting for approximately 2½ inches on either side of the midline. It is then ordinarily possible to close this incision with a midline suture. A small Penrose drain is left down to the cystotomy site through the stab wound, and a pressure dressing is applied. No catheters are left in the ureters or in the neourethra of the initial operation, and drainage is afforded solely by the cystotomy tube. In infant girls it is possible to reconstruct the entire urethra at this procedure. However, in male patients, repair of the penile portion of the epispadias is reserved for a later stage. It may be possible, as our technique improves, to accomplish all of this at one stage.

In the male, formation of the internal sphincter is more difficult because of the presence of the firm and fairly fixed prostatic portion of the urethra, and the muscle used for the internal sphincter in such cases is the trigone immediately proximal to the prostate. This technique requires more extensive undermining of the trigone than in the female and more care must be exercised to avoid damaging the ureters just lateral to the ureterovesical junctions. The cystotomy tube is removed 10 days postoperatively and the smallest possible Foley catheter is inserted via the urethra. The cystotomy wound is allowed to heal, and the urethral catheter is removed.

The patients should experience difficulty voiding initially and promptly establish residual urine. This is not necessarily bad. Part of the principle of the function of this sphincter is to force the bladder to hypertrophy, much as it does in older patients with benign prostatic hypertrophy or vesical neck obstruction resulting from an acquired cause. The difficulty of balancing a sphincter against the detrusor is too much of a challenge to surgical technique alone.

## REPORTS OF PATIENTS

PATIENT 1. This three week old baby boy was first examined on 11 June 1958 for evaluation and treatment of an exstrophy of the bladder noted at birth. Birth and development had been normal. Birth weight was 8 pounds. He had had no febrile illnesses. A flat film of the abdomen had shown no osseous abnormalities. The symphysis was typically separated.

On physical examination the exstrophied bladder was pink and edematous and rather small, measuring only 3 centimeters in diameter. The umbilicus was approximately 2 centimeters above the upper limits of the exstrophied bladder. Both testes were in the scrotum. The anus was anteriorly placed and there was only fair anal sphincter tone. There was no

evidence of palpable inguinal hernias on the initial examination. Intravenous urograms on this admission showed delayed appearance of the contrast medium bilaterally with a grade 3 hydroureteronephrosis, apparently on the basis of ureterovesical obstruction (Fig. 3).

Over the next 3 months the appearance of two large bilateral indirect inguinal hernias was noted with episodes of incarceration of the left inguinal hernia and, accordingly, this was repaired. At this time an attempt was made to invert the bladder and close the abdominal wall. However, the abdominal wound dehisced so that further attempts at closure were abandoned. In the following 2 months, the right inguinal hernia showed threats of incarceration on several occasions and was repaired through an incision made quite lateral and medial to the usual inguinal hernia incision, swinging beneath the inguinal ligament, inasmuch as it was believed important to preserve the abdominal wall skin for later undermining in reconstructing the midline. The blood urea was 35 milligrams per cent; the serum creatinine, 0.2 milligrams per cent; the serum sodium, 139 milliequivalents per liter; the serum potassium, 5.3 milliequivalents per liter; the $CO_2$ capacity, 24.3 millimeters per liter; the chlorides, 109 milliequivalents per liter; calcium, 10.4 milligrams per cent; and phosphorus 5.8 milligrams per cent. The hemogram was within normal limits. Urine specimens obtained from each ureter were negative on culture and showed 0 to 1 white blood cell per high-power field. There was a trace of protein.

On 10 July 1959 the bladder was again closed and recessed into the retropubic space. The patient was maintained on furadantin and had no residual urine prior to his dismissal. He remained afebrile and began to void in 15 to 20 cubic centimeter amounts at a time and would have dry periods for only a short time. In the interval he would have dribbling. He was studied in April 1960, 9 months after his reconstruction and found to have a bladder capacity of approximately 60 cubic centimeters. There was an intermittent leakage of urine from the neourethral orifice and only an occasional spurt of urine in amounts of approximately 10 cubic centimeters. Cystoscopy revealed the sphincteric area to be probably too lax. The tube was smoothly lined with urothelium and there was no evidence of stricture. The bladder mucosa had a normal appearance as did the ureteral orifices. A cystogram showed bilateral reflux with no change in the appearance of the right kidney. There was a marked regression in the left hydroureteronephrosis without evidence of pyelonephritis. He had had two episodes of fever lasting 1 to 2 days during the 8 month period. Findings from urinalysis and cultures were negative at this examination. The abdominal wall was well healed and firm (Fig. 4).

PATIENT 2. This 6 month old baby was examined on 28 November 1955 for evaluation and treatment

FIG. 4. Patient 1. Photograph of reconstructed abdominal wall 9 months postoperatively. The episadias has not yet been corrected.

of exstrophy of the bladder. He was the result of an intra-abdominal pregnancy delivered by cesarean section, at which time the entire fetus was found to be lying free in the peritoneal cavity with the head pressed and deformed against the sacrum. The child was found to have multiple congenital anomalies. These included exstrophy of the bladder, a large right indirect inguinal hernia, hypoplasia of the penis, and bilateral congenital dislocation of the hips. There was a question of hydrocephalus initially, but the condition was found merely to represent marked asynclitism, apparently due to prenatal pressure on the left side of the skull. There was no evidence of pulmonary or cardiac anomaly. An intravenous urogram showed normal renal architecture and collecting systems bilaterally without evidence of obstruction. Blood urea was 35 milligrams per cent and serum creatinine was 0.6 milligrams per cent. The hemogram was within normal limits. Findings from urine specimens obtained from each ureter by ureteral catheterization were entirely negative. Cultures were sterile.

On 6 December 1955 plastic reconstruction of the bladder and abdominal wall with formation of an internal sphincter from trigone was performed. The right inguinal hernia was repaired at the same time. Flaps of rectus sheath were used to reconstruct the abdominal wall, and treatment of the bilateral dislocation of the hips was instituted. After repair and healing of the cystotomy wound, the child dribbled small amounts of urine not in excess of 5 to 10 cubic centimeters at a time. In April of 1957 the epispadias was repaired. However, two small fistulas subsequently developed, one at the base of the penis and one in the distal third of the reconstructed urethra. The patient remained afebrile and showed little infection. He was carried on maintenance antibacterial therapy for a period of 8 months, after which this was

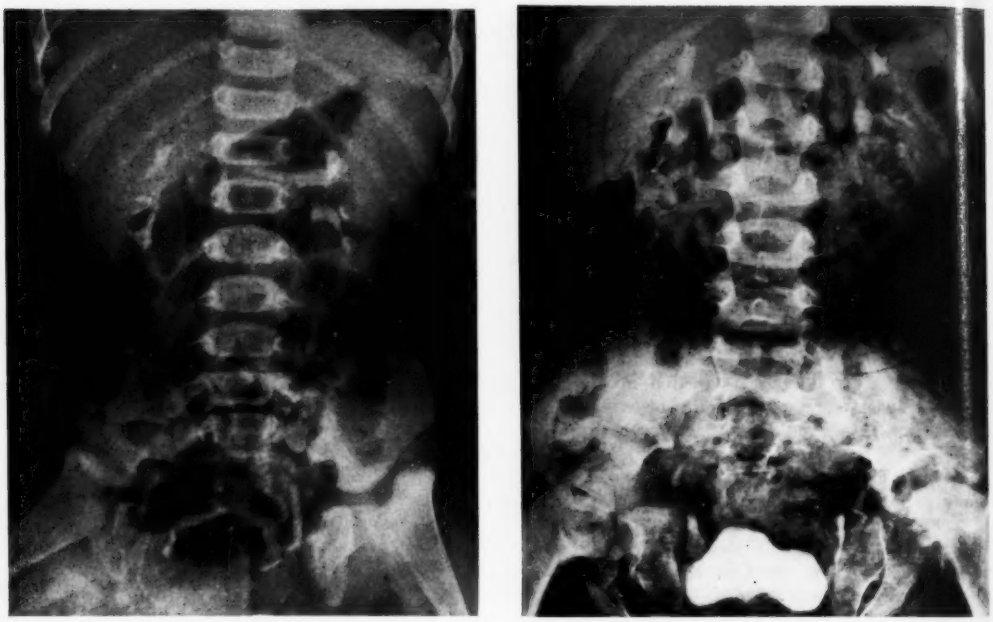

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FIG. 5.

*Legend and Figure 5c on following page.*

found to be unnecessary. His urine has remained clear. He was last restudied on 15 July 1959, at which time cystoscopy disclosed the vesical neck to be adequate but probably too lax. Intravenous pyelograms showed no change in the upper urinary tract (Fig. 5). Bilateral reflux to both kidneys was demonstrated on the cystogram. The cystographic shadow was not remarkable and represented approximately 90 cubic centimeters of contrast medium. With the patient supine there was no evidence of dribbling. Blood chemistries remained within normal limits. He was last seen 16 January 1960, and he was still noted to dribble, particularly upon standing. He is now voiding amounts of 30 cubic centimeters at a time.

PATIENT 3. An 11 month old girl was admitted on 18 November 1956 for diagnostic studies and a planned repair of exstrophy of the bladder. It had been noted at birth that there was exstrophy of the bladder as well as failure of fusion of the pubic symphysis. Birth and development had otherwise been normal.

Physical examination disclosed a small, irritable girl. The positive findings were limited to the abdomen and pelvis. There were no abnormal organs, tenderness, or masses in the upper abdomen. The lower abdominal wall showed the typical deformity of exstrophy of the bladder with an edematous mucosal surface of approximately 5 centimeters in diameter. The ureteral orifices could be easily identified. There was separation of the vaginal labia as well as the clitoris. The vagina showed a median septum. However, this was found to be merely a mucosal bridge and did not represent duplication of the vagina. There was a small, normal vaginal canal with a tiny cervix visible on panendoscopy. The rectum was anteriorly placed, and the hips were noted to be in marked external rotation because of the posterior position of the acetabula. The child was unable to stand and could not crawl. A chest film was not remarkable except for nonspecific bronchovascular accentuation. Intravenous urograms showed normal renal architecture and collecting systems bilaterally with prompt appearance of the contrast medium and no evidence of obstruction. There was noted to be a right lateral scoliosis based on a hemivertebra at the first lumbar level. The pubes were widely separated and the femorocapital epiphyses were in the acetabula. However, the slopes appeared to be steeper than usual. The hemogram was within normal limits. Catheterized urine specimens from each ureter showed 1 to 2 white blood cells per high-power field, but there were no bacteria on the stained sediment and the cultures were negative. The blood urea was 33.4 milligrams per cent and the serum creatinine 1.1 milligrams per cent.

Because of an episode of diarrhea associated with upper respiratory infection, repair was postponed

FIG. 5. Patient 2. a, Preoperative intravenous pyelogram showing normal upper urinary tract. Note the congenital bilateral dislocation of the hips. b, Postoperative intravenous pyelogram showing a normal upper urinary tract. Note the relatively normal V-shaped appearance of the reconstructed vesical neck. c, Cystogram showing good bladder capacity, bilateral reflux, and, again, the occluded neosphincter. The catheter had been withdrawn at this point and there was no leakage of urine with the patient in the supine position.

c

FIG. 5.

until 25 February 1957, at which time the bladder was closed, the abdominal wall reconstructed, and the vesical neck tightened around a filiform catheter. The postoperative course was uneventful. The cystotomy tube was removed on the sixteenth postoperative day at which time the bladder was examined under anesthesia via the cystotomy wound. The mucosa was intact. Suture lines were well healed. A No. 14 sound could be passed via the angulated urethra with some difficulty. A No. 8 Foley catheter was placed in the newly formed urethra. The cystotomy wound healed promptly. After removal of the urethral catheter 4 days later, the patient was unable to void and fever developed. Catheterization revealed a capacity of 90 cubic centimeters of urine within the newly formed bladder. An intravenous urogram disclosed acute dilatation of both ureters and both renal pelves (Fig. 6). She was maintained on catheter drainage and managed with antibacterial therapy. Catheter drainage was maintained for 1 month, after which the catheter was removed. She was afebrile and began to void small amounts of urine.

She was readmitted for study 26 months later. Development and growth had been normal. The abdominal wall was well healed. The urethral meatus could be seen at the most anterior portion of the reconstructed introitus. A voided urine sample showed 10 to 20 white blood cells per high power field and numerous bacilli. She walked quite well without evidence of limp but had a slightly waddling gait. Intravenous urograms showed normal renal architecture and function bilaterally. There was no remaining evidence of the postoperative hydroureteronephrosis. The bladder shadow was of normal size. The estimated bladder capacity was approximately 150 cubic centimeters, but there were numerous calculi 1 centimeter in diameter with radiolucent centers noted within the bladder. The appearance of the bladder was quite abnormal. The base of the bladder was quite low and, on cystography, there were two definite pouches which protruded well below the symphysis pubis (Fig. 7). The ureters were seen to enter the base of the bladder. Cystoscopy showed the urethra to be of adequate caliber. It could be dilated easily by a No. 21 F. catheter and, after removal of the cystoscope, the muscular tube could be seen to contract and completely occlude the opening. The bladder mucosa was intact throughout except for some minimal trabeculation. The trigone and base of the bladder fell away quite sharply from the vesical neck, forming a saddle bag type of basfond. The small calculi were crushed with a Coppridge forceps and removed. Bladder capacity was between 100 and 150 cubic centimeters on this examination. Ascendent lipiodol was instilled at the close of the procedure and, at the end of 1 week, approximately ½ of the originally instilled oil still remained in the bladder as evidence of persistent residual urine (Fig. 8). Cystoscopy was repeated 3 months later. The bladder still showed some bullous edema but no remaining calculi were found. Cystograms performed at this time with approximately 80 cubic centimeters of 5 per cent skiodan revealed bilateral ureteral reflux without evidence of hydronephrosis. There was no leakage from the bladder. During this period the patient was maintained on furadantin which she tolerated well. Calculi were reported as calcium oxylate. Six months later she was again examined. Urinalysis showed 10 to 20 white blood cells per high-power field with numerous bacilli. She had been afebrile for the past 6 months, and her mother reported that she managed to stay dry for periods of 2 to 3 hours and then voided with a good urinary stream. Her urinary control was not as good when she was tired. In watching the child urinate one cannot differentiate the mechanism from the normal. There is no increased straining or evidence of increased

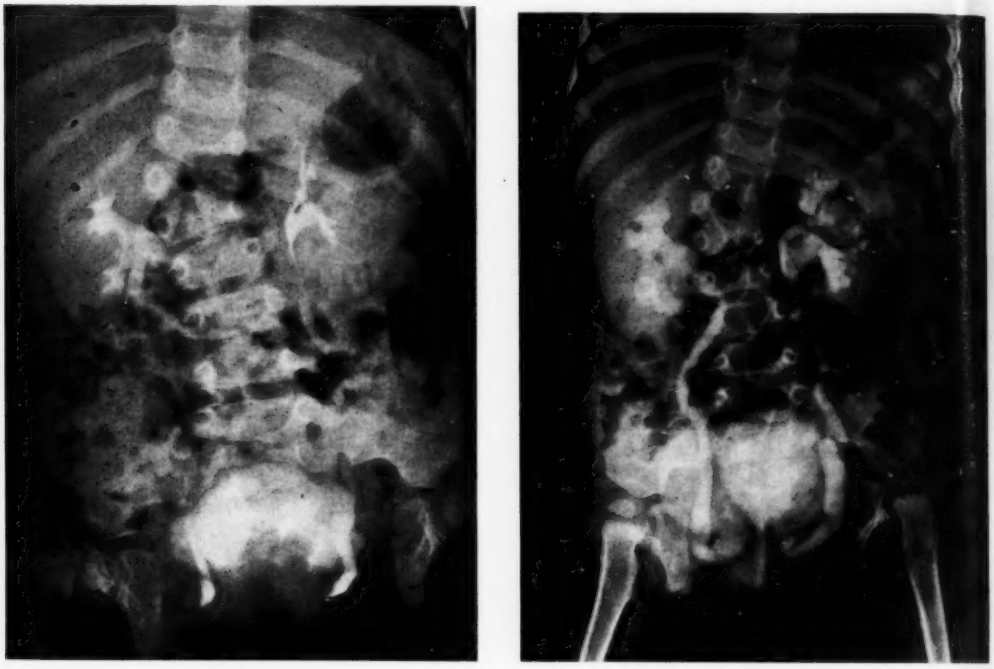

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FIG. 6.

FIG. 6. Patient 3. a, Preoperative intravenous pyelogram showing a normal upper urinary tract. Scoliosis and hemivertebra at the first lumbar level are visible. b, Bilateral hydronephrosis and dilated bladder 1 month postoperatively secondary to overocclusion of the vesical neck.

intra-abdominal pressure. There is good force and continuity to the urinary stream. A measured residual urine of 30 cubic centimeters was obtained after the child voided 90 cubic centimeters.

## COMPLICATIONS

A not unexpected postoperative complication was the persistence of residual urine and subsequent formation of numerous bladder calculi. This was not a result of the inability of the detrusor to compensate for the tightened vesical neck, but was caused by the formation of an artificial saddle bag shaped bas-fond behind the trigone, the abnormal course of the urethra, and the lack of firm perineal floor beneath the base of the bladder. This complication may require a change in the procedure. We are considering the division of the fibrous symphysis pubis, passing the urethra beneath it, and reapproximating the symphysisial band and soft tissues above it to obviate this complication. It may be possible to plicate the endopelvic fascia beneath the bladder also, which would be found to provide additional support.

All of these patients have been shown to have reflux of urine freely from the reconstructed bladders to the renal pelves and in 1 patient there is pre-existing hydroureteronephrosis. Even in the presence of reflux of residual urine, as in patient 3, there has been no evidence of progression of hydronephrosis nor episodes suggestive of pyelonephritis. This may be a result of maintenance therapy with antimicrobial drugs. In this respect, management is much like the treatment of chronic pyelonephritis in children with roentgenologically normal urinary tracts.

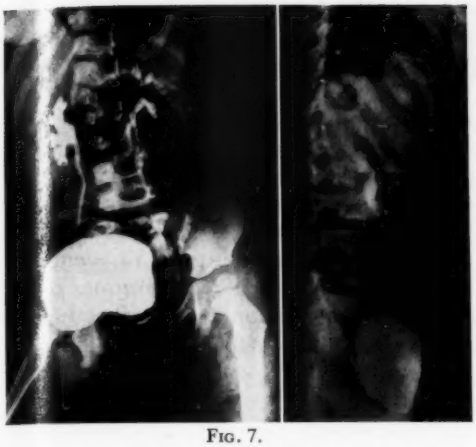

FIG. 7.

FIG. 7. Patient 3. Right posterior oblique and lateral cystograms made 30 months after operation. Bladder capacity is excellent. There is bilateral reflux with a mild right hydronephrosis.

FIG. 8.

FIG. 8. Patient 3. Persistence of ascendent lipiodol at 1 week which confirms the fact that residual urine is present.

The association of bilateral inguinal hernias in the males is a troublesome feature. However, the hernias can be corrected quite easily via low-placed inguinal incisions which do not compromise the skin of the lower abdominal wall. We prefer surgically unsullied skin for the reconstruction of the abdominal wall. These are not difficult hernias to repair. The external and internal rings are almost superimposed and, usually after the skin incision, the sac is found to be lying immediately beneath the subcutaneous tissue.

Bilateral congenital dislocation of the hips occurring in 1 patient was an interesting associated anomaly. There have been no marked gait disturbances in the other patients. Despite the fact that the pubes are not fused, the pelvic girdle in this condition forms a perfectly firm ring. These children are able to run, climb, and jump as well as their contemporaries. The problem does not seem great enough to warrant attempts at closing the pubis and there does not appear to be any particular virtue in approximating the pubis as far as urinary control is concerned. The reconstructed smooth muscle sphincter in our hypothesis is the single mechanism to be relied upon for continence.

## DISCUSSION

In returning to the detrusor itself as a sphincter mechanism, we are attempting specifically to correct it by reconstructing the normal mechanism of urinary control. This was suggested first by Young (13). His first case, without the aid of antibacterial agents or knowledge of reflux, was remarkably successful.

Methods of urinary diversion for the treatment of exstrophy have been, in general, unsatisfactory and it appears that further attempts at reconstruction are warranted in an effort to avoid severe renal damage from ascending infection, thus preserving physical life for these patients as well as providing them with a reasonable social existence. There is no question that numerous problems remain to be solved. As the operation becomes refined and revised it will be necessary to combine a reconstruction of the ureteral hiatus to prevent reflux in some cases. This is one of the most worrisome features in the reconstruction of the bladder. It can be said with a fair measure of confidence that it will be possible to control urine with a sphincter constructed of detrusor muscle, either as a tubed flap or as a plicated fold. In the studies of Lapides, his patients were able to urinate through

their tubed flap cystotomy sinuses at pressures comparable to normal voiding pressure in man. At resting pressures these tubes were capable of preventing the leak of urine.

Smooth muscle has the capacity for great extensibility and, at the same time, can retain its contractility, but in its resting state the individual fibers shorten to within a few fractions of a millimeter of their maximally contracted length. Oxygen consumption and lactic acid production of the cell is at its lowest—it is at rest. It is at this time that it functions as a closed sphincter, preventing the escape of urine. The passive mobility of the smooth muscle in the sphincteric areas seems to be the significant fact. The ability of the muscle when extirpated, denervated, or whatever—except dead—to return to a shortened resting length is the important thing. This is the singular beauty of opposing this muscle to itself. It is sort of a jujitsu trick—overcoming a greater force with itself.

The concept of a reconstructed urinary sphincter composed of smooth muscle is not a new one—merely a neglected one. The surgical techniques are available. Our knowledge of the physiology of micturition has become more complete and the control of urinary infection has become possible. The situation seems to be ideal for the imaginative use of smooth muscle as a sphincter in many of the most distressing congenital and acquired cases of urinary incontinence.

SUMMARY

Tubed flap urethras in dogs, when properly constructed, can be relied upon to conduct urine and provide continence.

Various methods were tried in a small series of dogs and these principles were then applied to sphincter construction in 3 patients with exstrophy of the bladder. The surgical principle in these instances is opposition of the smooth muscle of the bladder to itself. The reconstruction of an internal sphincter mechanism is accomplished by undermining trigone and vesical neck, approximating this in a circular manner, and plicating it to occlude its lumen at a single point. A description of the operative technique is given and results in 3 patients are discussed. Theoretical considerations of the mechanism of function in the neourethra are considered and further applications are projected.

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# PERFUSION OF COMPOUNDS POTENTIATING RADIATION FOR THE THERAPY OF CANCER

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TWO FORMS OF THERAPY for cancer exist today—surgery and chemotherapy. Radiation therapy in clinical use is a form of chemotherapy based largely on the attack by atoms and free radicals against cancer cells. Atoms and free radicals are the main reactive chemical agents formed by interaction of ionizing radiation with ubiquitous body water and directly with vital proteins and nucleic acids. Subsequently, the atoms and free radicals interact with cellular and extracellular components to produce radiation effects recognized clinically. Thus at the level of the irradiated cell, a beam of radiation devolves largely to a series of chemical reactions, in which highly reactive atoms and free radicals such as hydrogen atoms, $OH\cdot$ and $HO_2\cdot$ radicals, radicals from direct action of irradiation on vital large molecules, as well as peroxides and their decomposition products are first formed and then damage the cell.

Radiation therapy is here classified as a form of chemotherapy to focus attention on potential methods of surgical and chemical manipulation of the basic chemical reactions underlying therapy by ionizing radiation: roentgen-ray and supervoltage therapy; therapy with alpha, beta, and gamma emittors and neutron bombardment, for example.

Two mechanisms suggest themselves for enhancing the biologic effects of atoms and free radicals formed by irradiation: the first to increase their total number and biologic efficiency, the second to remove the chemical protectors against irradiation and scavengers of free radicals present in irradiated tissue. The first involves changing the type or amount of radiation given, mechanisms which have obvious clinical limitations for immediate application.

The removal of chemical protectors against irradiation and of free radical scavengers from the area of the tumor prior to irradiation appears to be the more fruitful point of immediate surgical and chemical attack for enhancing the effects of many types of radiation against cancer, including ordinary roentgen-ray and supervoltage therapy for rapid clinical application.

Nothing would be gained by entering here into the controversy about the relative importance of the direct and indirect effects of irradiation because of the fortunate similarity of their surgical and chemical implications. Suffice it to say that the differences between the mechanisms of action of ionizing radiation will be essentially quantitative since free radicals from proteins and nucleic acids can be formed by interaction of proteins and nucleic acids with indirectly formed $OH\cdot$ radicals or by direct action of the radiation on proteins and nucleic acids. Also, Gordy and Miyagawa have pointed out that cysteine and cysteamine may be uniquely effective as protectors of protein against direct effects of radiation because of the multiplicity of requirements which such protectors against direct effects must meet and which cysteine and cysteamine do meet. From a consideration of both indirect and direct effects of irradiation, therefore, decreasing the activity of the sulfhydryl scavengers of free radicals in tumors, especially of cysteine, prior to irradiation, appears to be a valid

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Aided by grants from the U. S. Public Health Service (H-5186 and C-2282), from the Department of Surgery, Presbyterian-St. Luke's Hospital and the Knock Research Foundation.

point of surgical and chemical attack on cancer.

Kharasch and associates and Scholes and Weiss as well as many others have documented a tremendous array of reactions effected by atoms and free radicals in solution-dimerization, polymerization, dismutation, and anti-Markownikoff addition reactions, for example. All such reactions should be encouraged by inactivating the sulfhydryl scavengers of free radicals and especially cysteine, present in tumor before irradiation of tumor.

Perfusion and infusion intra-arterially to tumor bed of a variety of antisulfhydryl compounds—arsenicals, mercurials, and iodoso compounds, for example—thus appeared desirable surgically to shift the reactions of atoms and free radicals generated by irradiation toward irreversible denaturation of protein and consequent cell death in the tumor.

The reversibility of the reactions of sulfhydryl compounds with their inhibitors dictated other steps in the program. Sulfhydryl groups are known to be essential for a variety of reactions involved in metabolism of foodstuffs, generation of high energy phosphate bonds, and anabolism. Such reactions are partially inhibited by radiation and should be further inhibited by perfusion and infusion of antisulfhydryl compounds into tumor bed before irradiation. The inhibition, unfortunately for patient and surgeon, however, is reversible so that the cancer cells will escape the effects of the inhibition. Help should be sought wherever possible, therefore, from other reagents known to inhibit the same reactions.

As a result, inhibitors of multiple anabolic and metabolic paths should be tested concurrently with antisulfhydryl compounds: inhibitors of glycolysis, the tricarboxylic acid cycle, and respiratory enzyme systems, especially cytochrome oxidase; inhibitors of transaminations; agents uncoupling phosphorylation as well as compounds known to inhibit anabolic reactions to deoxyribonucleic and ribonucleic acids, such as purine and pyrimidine antimetabolites, the antifolics, and the actinomycins.

Finally, because this program is part of a larger one involving antibodies against tumor and their complexes with various cytotoxic materials including sulfhydryl inhibitors, described previously (12, 13), the dose of radiation to be potentiated through perfusion and infusion of chemicals was deliberately chosen to be low in the preliminary work.

The unsolved problem in the surgery of cancer is the handling of the cancer cells outside the field of surgical attack which cause distant metastases. One of the best and cheapest methods of handling these for the patient may be the use of autogenous vaccines. Further, one of the central problems in the use of antiserums in general and also in the use of cytotoxic colloids peptized by antibody against tumor is increasing the permeability of capillaries to antibodies and to colloidal particles peptized by antibodies against tumor. Physical methods such as roentgen-rays, diathermy, and other electromagnetic fields should be tested for increasing capillary permeability along with the chemical methods previously discussed (13).

Erythema doses of roentgen-rays are in the range of 1,000 roentgens or less. Therefore, the preliminary program was set up to find a combination of chemicals binding sulfhydryl compounds along with various other antimetabolites blocking multiple metabolic and anabolic paths which would be injurious to tumors at roentgen-ray doses totally 600 to 900 roentgens. If such combinations could be found, they obviously would have widespread application with other types and doses of irradiation, alone and in combination with autogenous vaccines and with chemically modified antibodies against tumor. If sufficiently specific antibody complexes could be formed with chemicals potentiating irradiation, the patient ultimately might be treated with such antibody complexes plus very low doses of whole body irradiation.

METHODS

The V-2 tumor in rabbits was used first as the test system. Because of the large number of chemicals to be tested, an agar plating technique was used to screen the chemicals to be injected into the rabbits. The method used was similar to the agar plate assay technique described by DiPaolo and Moore with several changes. A medium known to support the growth of ascites and other cancer cells in the cytogenerator was used, Eagle's basal medium containing essential and nonessential amino acids plus vitamins as well as 10 per cent rabbit serum and 10 per cent fetal bovine serum. Also, after the cancer cells were removed from the animal, they were immediately exposed to the chemicals on paper discs, for 3 to 4 hours at 37 degrees C. with no period of intermediate cooling, and then immediately tested for redox activity.

Of the redox indicators suggested by Di Paolo and Moore, only methylene blue has been used. Triphenyltetrazolium chloride gave too feeble a color change with viable tumor to allow any differentiation between living and potentially dead cells. With the indophenols, several of the antimetabolites tested, such as o-aminophenol, o-phenylene diamine, and mapharsen, reacted directly with indicator to give false negative results.

Drugs were applied to the test discs in amounts related to the median lethal dose of the drug. The following amounts of drugs were applied to discs for use in the tests to be reported unless otherwise indicated: nitrogen mustard (HN2), 0.1 milligram; methotrexate, 0.2 milligram; mapharsen and other sulfhydryl inhibitors, 0.1 milligram except mercuric succinimide at 0.3 milligram; sodium fluoride, 0.65 milligram; sodium malonate, 3.0 milligrams; sodium azide, 0.005 milligram; o-phenylene diamine lactate, 4.0 milligrams; ammonium lactate, 10 milligrams; sodium pyruvate, 10 milligrams; 5-fluorouracil, 0.5 milligram; actinomycin D, 0.001 milligram; hydrocortisone, 5.0 milligrams, and combinations of 4 milligrams of ammonium lactate, 4 milligrams of sodium pyruvate, and 2 milligrams of sodium glutamate per disc.

Perfusion of chemicals in rabbits was carried out by using the pump oxygenator previously described (11) which is small enough to be primed by the animal's own blood to avoid difficulties from vasospasm. When it became evident that results were good enough probably to show up without perfusion and also that multiple doses of irradiation and multiple doses of chemicals after irradiation would be desirable, work was continued with the Ehrlich ascites tumor implanted subcutaneously in Strong A mice.

A standard inoculum of $2\times10^6$ ascites cells administered subcutaneously was used for producing the tumor, a dose previously found to give 100 per cent takes. In each experiment after inoculation of the ascites cells, mice were divided into at least 3 groups, each group consisting of 8 mice. One control group received only intraperitoneal tranquilizer at the time of irradiation of the other animals. One group received only roentgen-ray therapy as a second control. One or more groups received chemicals in addition to roentgen-ray therapy. The sulfhydryl inhibitor mapharsen was used in this preliminary work at a dose of 4 milligrams per kilogram intravenously 3 to 4 hours before irradiation. All irradiations were preceded by intraperitoneal injection of nembutal at 15 milligrams per killogram to tranquilize the animals enough to allow their fixation under lead shields.

Irradiation was given either in 2 doses of 450 roentgens each on 2 successive days or in 3 doses of 300 roentgens each on 3 successive days. Irradiations were started on day 3 after implantation of tumor on day 1. A 250 kilovolt unit was used for the irradiation at 15 milliamperes, 0.5 millimeter copper and 1.0 millimeter aluminum filter, 1.5 millimeter copper half value layer, 50 centimeter target distance and 65 roentgens per minute or a 200 kilovolt unit at

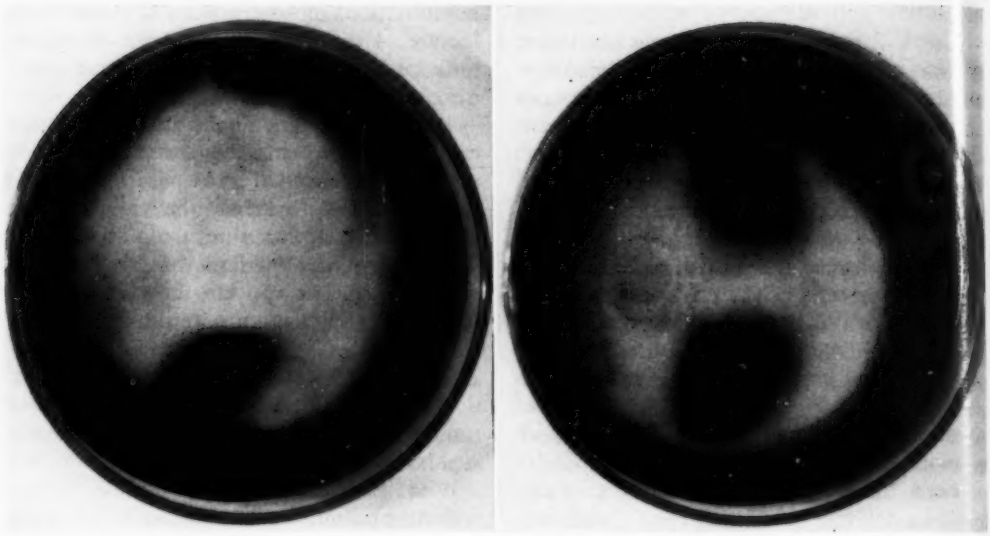

FIG. 1. Effects of radiation on activity of several antimetabolites. The plate on the left received no radiation; the plate on the right, 600 roentgens of radiation. Marpharsen at 12 o'clock became active against V-2 cells by combination with irradiation.

18 milliamperes, 0.5 millimeter copper and 1.0 millimeter aluminum filter, 1.5 millimeter copper half value layer, 50 centimeter target distance and 65 roentgens per minute.

Antimetabolites used for postradiation treatment were injected intraperitoneally 30 to 60 minutes after irradiation, starting with the first day of irradiation and continuing for 7 days. Dose levels used were: mapharsen, 0.5 milligram per kilogram; sodium fluoride, 6.5 milligrams per kilogram; sodium malonate, 30 milligrams per kilogram; sodium azide, 0.05 milligram per kilogram; o-phenylene diamine lactate 40 milligrams per kilogram; ammonium lactate, 50 milligrams per kilogram; 5-fluorouracil, 5 milligrams per kilogram; and actinomycin D, 0.005 milligram per kilogram.

The mice were weighed weekly and their tumors calipered in two dimensions. Degree of tumor inhibition was graded according to the following system: (−), no effect, tumor growth to ¾ or more of the average diameter of the controls; (+), slight inhibition, tumor growth from ½ to ¾ of the average diameter of the controls; (++), fair inhibition, tumor growth from ¼ to ½ of the average diameter of the controls; and (+++), moderate inhibition, growth to less than ¼ of the average diameter of the controls.

For the irradiation, mice were affixed to the same shields previously described for the neutron capture therapy of tumors (14). These boron carbide methylmethacrylate boxes were here used just as convenient holders for the animals which would not traumatize the tumors. Flexible lead sheets, 5 millimeters thick, were used as the actual shield against roentgen-rays and cut to fit the area of the tumors. Eight mice were irradiated simultaneously through a 20 by 20 centimeter field, with the tumors placed centrally to avoid fall-off at the periphery.

Preliminary work showed that palpation of the tumors on the third day was too poor a guide to the large area where tumor eventually arose, to allow any effects of irradiation to be shown. For the experi-

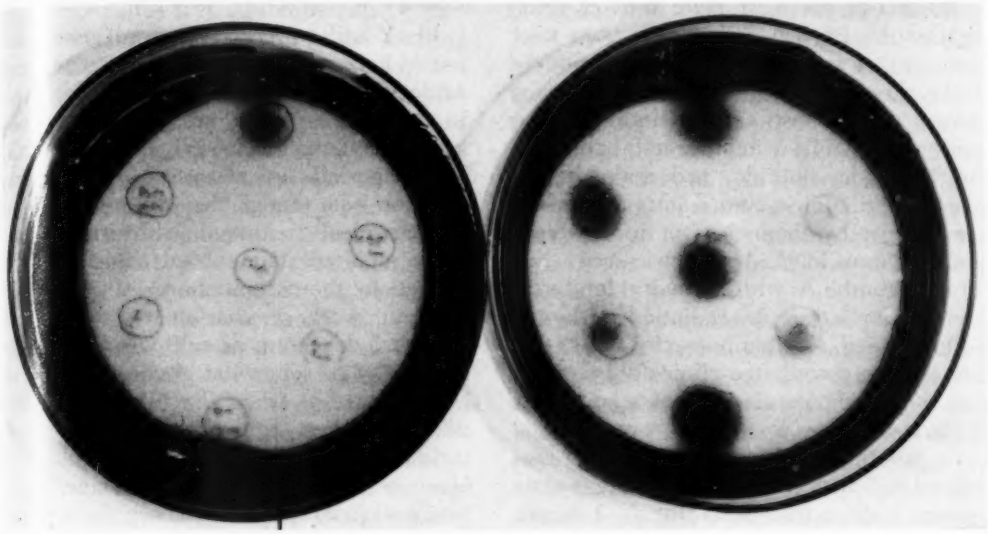

FIG. 2. Effects of radiation on activity of various sulfhydryl inhibitors. The plate on the left received no radiation; the plate on the right, 600 roentgens of radiation. The activity of several of the compounds was potentiated by irradiation.

ments to be reported, consequently, the area of injection of the inoculum of ascites cells was encircled at the time of injection by a marking solution of aqueous picric acid. The lead shield was then cut to fit these picric acid marks without any attempt being made to palpate tumor on the third day.

RESULTS

Figure 1 shows the results of agar plate tests against the V-2 tumor from rabbits. A positive test shows up as a dark spot under the area to which drug was applied. In both of the petri dishes, 5 drugs were tested: mapharsen at 12 o'clock; mercuric succinimide at 7 o'clock, and nitrogen mustard (HN2), methotrexate, and hydrocortisone hemisuccinate at intermediate positions. The toxic mercuric succinimide was deliberately used at an inordinately high dose to show some activity and 1 dark area on the first plate. The plate on the left received no irradiation; the plate on the right, 600 roentgens.

In the left plate, after 12 hours, only the highly toxic mercuric succinimide showed any activity. In the irradiated plate on the right, the sulfhydryl inhibitor mapharsen became active by its combination with roentgen-rays. Nitrogen mustard, methotrexate, and hydrocortisone were inactive both with and without radiation as was 600 roentgens of roentgen rays alone.

Figure 2 shows results of testing a group of sulfhydryl inhibitors against the V-2 tumor. Again the plate on the left received no irradiation, while the plate on the right received 600 roentgens. All drugs were used at 0.1 milligram per disc except for p-chloromercuribenzene sulfonic acid at 1.0 milligram per disc at 12 o'clock. Other drugs tested were: mapharsen in the center; p-chloromercuribenzoic acid at 2 o'clock; p-arsenosobenzoic acid at 4 o'clock; gamma (p-arsenosophenyl)butyric acid at 6 o'clock; o-iodosobenzoic acid at 8 o'clock; and p-chloromercuribenzene sulfonic acid at 0.1 milligram per disc at 10 o'clock. The increase in effectiveness of several of these sulfhydryl inhibitors by combination with low doses of irradiation is obvious.

Results of the agar plate tests of drugs against the Ehrlich ascites cells from mice were similar to the results obtained with the V-2 tumor from rabbits. The results of many dozens of these tests can be summed up by stating that while 5-fluorouracil; actinomycin D; azide, fluoride, and malonate; o-phenylene diamine, and lactate all showed some effect by themselves or in combination, the most marked effect was seen when all were combined with sulfhydryl inhibitors such as mapharsen plus radiation. Although 5-fluorouracil and actinomycin D are believed to be potentiated clinically by radiation, no such potentiation was seen in any of the agar plates.

In general, the animal tests in vivo correlated well with the results of the agar plate assays. Rabbit tests with the V-2 tumor showed promise similar to the mouse tests to be described but inaccuracy of palpating this intramuscular tumor prevented accurate grading of tumor inhibition.

Eight series of mice were run, with 3 or more groups in each series and with 8 mice in each group. Irradiation alone gave a 1+ effect at the end of 1 week, fading to zero thereafter. The sulfhydryl inhibitor mapharsen at 4 milligrams per kilogram 3 to 4 hours prior to irradiation gave a 2+ effect in 3 series at the end of the first week, fading thereafter. When mapharsen prior to irradiation was combined with post-radiation mapharsen, fluoride, azide, and malonate or with lactate plus mapharsen, fluoride, azide, and malonate or with these 5 plus o-phenylene diamine lactate, 5-fluorouracil, and actinomycin D, the effect was 3+ at the end of the first week, fading to 1 to 2+ at the end of the second week and lower thereafter. As expected, the most marked effect and also the most marked weight loss, up to 10 per cent, were seen when all the drugs were combined. In some animals, the entire series of drugs could not be tolerated for 7 days without dangerous weight loss so treatment was of necessity terminated earlier.

No cures were effected.

## DISCUSSION

Black and coworkers have suggested the use of iodoacetate, fluoride, malonate, and azide to inhibit multiple enzymes involved in glycolysis and alternate paths for carbohydrate metabolism used by the cancer cell. They reported clinical success with the combination even though they did not combine the chemical treatment with irradiation. They reported that normal tissue was not injured by the combination.

In our work, mapharsen was substituted for the iodoacetate as sulfhydryl inhibitor because of its somewhat greater activity in agar plate tests when the two were tested side by side at equivalent proportions of their median lethal dose. While mapharsen alone or its combination with azide, fluoride, and malonate showed only slight effect without irradiation, the effect could be increased significantly by even low doses, 600 roentgens, of radiation.

When combined with irradiation of the ascites carcinoma in mice, some effect of the 4 drugs could be seen but not enough even with irradiation. Black and coworkers tried to potentiate the effects of the combination of iodoacetate, azide, fluoride, and malonate by combining this with cysteine and glutathione.

Both cysteine and glutathione, however, partially inactivate iodoacetate just as they do with mapharsen and other sulfhydryl inhibitors on our agar plate tests. The same effect has been seen by Roosa and De Lamater who found that 6-mercaptopurine inhibits the effect of mapharsen against cancer cells. The suggestion by Black and coworkers to combine sulfhydryl compounds with sulfhydryl inhibitors was therefore rejected.

Administration of sulfhydryl compounds will, however, play an important part in the clinical application of our program already outlined. In mice, the dose of sulfhydryl inhibitor administered intravenously prior to radiation was limited to a fraction of the median lethal dose for obvious reasons. In humans, by contrast, large amounts

of proper sulfhydryl inhibitors can be perfused or infused through the cancer-bearing area while the rest of the body is protected by administration of specific antagonists for the excess sulfhydryl inhibitors used. Thus, 2,3-dimercapto-1-propanol (BAL) is a specific antagonist for arsenicals and mercurials, for example, and is commercially available for intramuscular administration. Therefore, BAL given intramuscularly can be used as a specific antidote for the excess sulfhydryl inhibitor perfused or infused through tumor, as can thiomalate.

In this use of sulfhydryl inhibitor perfused or infused into tumor bed before irradiation with the patient protected from the toxic effects of excess sulfhydryl inhibitor by intramuscular BAL, this part of the program is somewhat analogous to the infusion of methotrexate to tumor with protection of the patient by intramuscular citrovorum factor, as advocated by Sullivan and associates.

It is to be specifically understood, however, that the sulfhydryl inhibitors are not to be relied upon for full cancerocidal effect but are to be used with radiation if possible and with other antimetabolites. In a previous article (13), I stated incorrectly that if derivatives of arsenic and other sulfhydryl inhibitors were to be used clinically, no irradiation of the patient would be used. The data in the present article point up the fact that alone the sulfhydryl inhibitors are not as active as they are in conjunction with irradiation. For clinical application, therefore, sulfhydryl inhibitors such as arsenic derivatives will be perfused or infused to tumor-bearing area and the area then irradiated for maximum effects. If the patient has already been irradiated to full tolerance, however, the sulfhydryl inhibitors in combination with a variety of other antimetabolites will be infused, since some of the combinations even without irradiation have shown fairly potent effects against tumor cells.

Even with irradiation, almost certainly other enzyme inhibitors blocking multiple metabolic and anabolic paths must be used clinically in conjunction with the sulfhydryl inhibitors. One such group was suggested by the early observation in the agar plate tests that even the bis sulfhydryl compound BAL did not inhibit completely the effects of large doses of the antisulfhydryl mapharsen which is p-arsenoso-o-aminophenol. Mapharsen contains also an ortho-aminophenol group in addition to the antisulfhydryl arsenoso group.

Therefore, o-aminophenol itself was tested and found to show activity against cancer cells, an effect possibly related to its ability to form Schiff bases with aldehydes and hence to act as a competitive inhibitor of pyridoxal phosphate in transamination reactions. To increase the effect, o-phenylene diamine was tested and found to have considerably greater effect. Reaction of this and other arylene diamines with the bis aldehyde glyoxal, for example, to form the quinoxaline proceeds within seconds at room temperature. As a result of its toxic effect against ascites cells in vitro, o-phenylene diamine was incorporated into the mixture used in the postirradiation treatment. Other substituted arylene diamines, such as, the bis chloro derivative, are being investigated for the same purpose. These aromatic amines may of course interfere with cell metabolism via other mechanisms besides transamination, such as amine oxidase reactions, but the important fact for the work is that they do interfere. Isonicotinic hydrazide (INH), tested and found to be less active in the agar plate tests was not used.

A second way to achieve competition with pyridoxal may be the use of unnatural aldehydes, especially dialdehydes like glyoxal and its homologues, to replace the pyridoxal in Schiff bases with the natural amino acids. Glyoxal, for example, has shown the expected activity against cancer cells in our agar plate tests so that this compound and other mono and disubstituted aldehydes as well as unstable adducts formed with the mono and poly aldehydes should be considered also for clinical application.

Because the early effects of roentgen and other ionizing radiation consist primarily of inhibition of deoxyribonucleic acid (DNA) synthesis, compounds inhibiting ribonucleic acid (RNA) synthesis and protein synthesis appeared to be desirable for this program. The actinomycins are reported by Goldstein and associates to inhibit RNA and protein synthesis, so were incorporated into the postradiation treatment when found to show activity in our agar plate tests against cancer cells.

Purine and pyrimidine antimetabolites would be expected to contribute also to cancerostatic effects because of their interference with anabolic reactions. Thus, such purine and pyrimidine antimetabolites as 5-fluorouracil, azaserine, and 6-diazo-5-oxo-1-norleucine should be useful. In the agar plate tests, 5-fluorouracil was found to contribute significantly to the effect of sulfhydryl inhibitors plus irradiation, so was incorporated into the postradiation treatment.

Because the program was set up with the probability in mind that for clinical use the antimetabolites would be infused to tumor bed over a protracted period of time, so that room temperature stability would be needed, the unstable diazo compounds were not used in this preliminary work. For rapid, intra-arterial injection to tumor, however, they may well be useful.

Lactate, pyruvate, succinate, and glutamate were investigated because of the report by Barron that inhibition of oxygen uptake postradiation was decreased by the presence of pyruvate, succinate, and glutamate, all requiring sulfhydryl containing enzymes for their metabolism. In rats made nephritic by propylene glycol, oxygen uptake was also found to be decreased by the presence of lactate, pyruvate, and alanine. With the animal tumors studied in our laboratories, lactate alone was more inhibitory when combined with radiation than mixtures of lactate, pyruvate, glutamate, and succinate although the opposite has been true in preliminary studies with human cancer cells. Because of the inhibitory effect of lactate against the V-2 and Ehrlich ascites cells in our agar plate tests, lactate was incorporated into the postradiation treatment of the animals.

Nitrogen mustard (HN2) was tested in the preliminary work because of its actions as an antisulfhydryl compound as well as an inhibitor of hexokinase and pyruvate oxidase and inactivator of DNA. The antifolic methotrexate was tested because of the evidence of Guggenheim and associates that the inhibition of formate incorporation and DNA formation following irradiation probably do not proceed through interference with metabolism of the provitamin folic acid or its tetrahydro derivative, citrovorum factor. It was hoped, therefore, that since the antifolics apparently interfere with formate use and biosynthesis of nucleic acid through a different mechanism from the one hit by irradiation, that the antifolics might exert a synergistic effect with radiation.

In the preliminary work with animal tumors, such as is seen in Figure 1, neither the alkylating agents, HN2 or TEM, nor the antifolic methotrexate appeared to give enough effect to warrant incorporation into the mixture of antimetabolites finally used.

With any human tumor, however, against which the alkylating agents or antifolics appeared to show synergistic effects, we would not hesitate to use them clinically along with the antisulfhydryl compounds plus irradiation. These three groups of compounds, antisulfhydryl compounds, antifolics, and alkylating agents, are particularly attractive for surgical use against cancer since they can be perfused or infused to tumor bed while the patient is readily protected from the effects of excess reagent by use of specific antagonists. The same sulfhydryl compounds, such as BAL and cysteine, which can be used to protect against sulfhydryl inhibitors like the arsenicals and mercurials can also be used to protect against rapid acting alkylating agents.

Throughout the work reported in the foregoing, the sulfhydryl inhibitor alone was

given prior to irradiation and the rest of the antimetabolites were given after radiation. There are several reasons for this. Substrates such as lactate and pyruvate may be an excellent protecting agent against irradiation, an effect borne out by our agar plate tests. Also, compounds containing aromatic hydroxyls and primary and secondary amine groups, for example, react avidly with atoms and free radicals. Hence they act also as scavengers of free radicals, just as do free sulfhydryl compounds, to inhibit the desired radiation damage mediated through atoms and free radicals. Thus, para-nitrophenol, tested because of its ability to uncouple phosphorylation, partially cancelled the benefits of sulfhydryl inhibitors plus radiation, in large part because of the presence of the phenolic hydroxyl.

To simplify the program as much as possible, therefore, azide alone was used to uncouple phosphorylation chemically as well as to inhibit cytochrome oxidase. Also, primary and secondary amines and phenolic hydroxyls were avoided when possible. Since some of the enzyme inhibitors and antimetabolites of necessity contained such groups, the whole group was given after radiation to avoid interference with the beneficial effects of antisulfhydryl compounds plus radiation. In the future, much work must be done on proper timing of the various antimetabolites, before and after radiation.

Just as para-nitrophenol inhibits radiation effects, so mapharsen itself which is p-arsenoso-o-aminophenol is an inadequate sulfhydryl inhibitor for combination with radiation for clinical cancer therapy since mapharsen also contains an aromatic hydroxyl as well as an amine group, both of which are free radical scavengers. The effects of the inhibition by the phenol and primary amine groups can be seen clearly in agar plate tests where high concentrations of mapharsen cancel the beneficial effects of the sulfhydryl inhibitor from the arsenoso group plus radiation. This dual effect, of increase in activity with radiation at low concentration of mapharsen and decrease in activity with radiation at high concentration of mapharsen, has been seen still more clearly in tests with human cancer cells.

As a result, an active synthesis program has been undertaken in our laboratories to prepare adequate sulfhydryl inhibitors which do not contain groups acting as free radical scavengers but are solubilized by groups known to promote free radical reactions. While phenols and primary and secondary amines should be avoided, various tertiary amines are quite useful. Some of these have actually been used industrially by Knock and Glenn (15) as promoters of free radical reactions catalyzed by peroxides.

To force more rapid uptake of sulfhydryl inhibitors in each passage through tumor bed on perfusion or infusion, sulfhydryl inhibitors are also being combined with mustard groups in the same molecule. While such compounds will be taken up more completely and rapidly on passage through tumor bed, especially if used with hyperthermia, linkage of antisulfhydryl groups, such as As = 0, to mustard groups, such as $-N(CC\ Cl)_2$ in the same molecule will limit amount of sulfhydryl inhibitor which can be perfused or infused to tumor bed because of the vesicant action of the mustard group on normal tissue. As a result, such antisulfhydryl-mustard combinations will be supplemented also by antisulfhydryl compounds linked simply to proper tertiary amines of the type which can promote free radical reactions, or solubilized by simple anionic groups such as carboxyl. To increase uptake of sulfhydryl inhibitor on each passage through tumor bed, sulfhydryl inhibitors, such as As = 0, -HgR, are also being incorporated into blood red azo dyes with high van der Waals forces and high tissue affinity, especially for cell nuclei.

The activity of p-chloromercuribenzenesulfonic acid suggests other leads for the synthesis program. If similar results can be obtained with sulfhydryl inhibitors joined to multiple polar groups by stable and un-

stable bonds, a good way will be available to gain further preferential attack against tumors since such polar molecules concentrate in the depolymerized ground substance about rapidly growing tumors. Brain tumors, especially the glioblastomas, will probably be the most susceptible to such attack.

Just as better sulfhydryl inhibitors are being prepared for this program, so more effective antimetabolites must continually be sought to block more effectively other metabolic and anabolic reactions used by the cancer cells. A large variety of purine and pyrimidine antimetabolites must be evaluated. Thus, only 5-fluorouracil was used in this preliminary work. More and better purine and pyrimidine antimetabolites can doubtless be used, as well as their nucleosides and nucleotides, especially "fraudulent" ones in which an unnatural sugar, such as an amine substituted sugar, is used in place of the natural sugar.

At every block in metabolism and anabolism which has been investigated in this preliminary work, improvement can unquestionably be achieved. Thus many compounds uncoupling phosphorylation besides azide should be tried. Fluoroacetate was tried as an additional inhibitor of the citric acid cycle in this work and discarded for these particular tumors but not for all. The effects of a variety of steroids should be investigated, although hydrocortisone did not prove useful in this early work. Colchicine was tried in one series of mice with Ehrlich carcinoma and showed no effect with sulfhydryl inhibitors plus irradiation, but with other tumors the effect might be quite different. There never would be hesitation in using the antifolics and alkylating agents in combination with sulfhydryl inhibitors plus radiation for any tumor against which the compounds showed activity in vitro. Because of the variability in reaction of individual members of a given tumor type, surgeons must continue to evaluate a whole spectrum of chemicals, alone and with radiation, for cancer therapy.

The dose of irradiation to be used for this program can probably be higher than the 600 to 900 roentgens used in this preliminary work. The Grahams have already noted that radiation therapy and autogenous vaccines appear to potentiate each other. One possible explanation may be that radiation therapy early causes increased vascularity and increased capillary permeability allowing easier passage of the large globulin antibody molecules across capillary barriers into tissue spaces to act on tumors. Exactly how high a dose of radiation can be used before radiation fibrosis decreases vascularity is not known.

To borrow data from the field of coronary artery disease in which vascularity effects are of tremendous practical importance to surgeons, it should be noted that Senderoff and associates have advocated the use of 2,000 roentgens to the myocardium to increase coronary arterial collateral circulation. While the use of radiation to the heart is not advocated for coronary artery disease because lasting benefits have not been noted in animals, some of our own data might be used to support the contentions of Senderoff and associates. Cardiac irradiation and other procedures have been tested in our laboratories by application of carefully chosen constrictors (10) to coronary arteries in dogs and subsequent determination of myocardial blood flow by use of radioactive tracers (16). Only 1 irradiated animal survived constriction of coronary arteries, but in this animal flow values were surprisingly normal 2 months later. At 4 months, however, the dog died suddenly, presumably from fibrillation since no other pathologic condition was found at autopsy. While protection was not permanent, at least at 2 months a dose of 2,000 roentgens was not harmful to the vascularity of the heart.

Correspondingly, even for combinations of antitumor drugs with autogenous vaccines and antisera in general, with which vascularity and capillary permeability of tumor bed are of prime importance, it may be possible to push radiation doses towards

2,000 roentgens or higher. If therapy with antiserums is abandoned, as for example in the case in which the patient cannot form a significant titer of antibodies, radiation fibrosis will be of less concern, so that radiation can be carried to the limit of tolerance by normal tissue.

Although no difficulties were noted in animals with low doses of radiation, the antisulfhydryl compounds will probably change the radiation tolerance of normal tissue as well as of tumor. Whether the net change will be to increase or decrease the relative sensitivity of tumors presently radioresistant can be answered only by careful clinical work. It may be possible to gain an idea of the minimum radiation dose necessary for a given patient by consideration of the results of in vitro assays of various chemicals combined with radiation against the given patient's tumor.

Time and again throughout this program the necessity arises for an in vitro assay of drugs with and without irradiation against a given patient's tumor for rational chemotherapy. Thus, there can be no truly specific sulfhydryl reagent, since the milieu of the sulfhydryl compounds in the individual cell determines such highly important factors as steric availability of the sulfhydryl groups. Therefore, a spectrum of sulfhydryl inhibitors must be assayed against an individual patient's cancer cells, alone and with radiation. Also, more and better antimetabolites must be sought to be used with the sulfhydryl inhibitors plus irradiation. Again, various types and doses of radiation must be evaluated.

These problems focus attention on proper handling of the cancer cells in vitro. Puck's feeder layer technique has been useful for supporting the growth of individual delicate cancer cells. For the surgical and chemical work described in the foregoing, however, it is less desirable because it introduces a contaminant of living, respiring Hela cells. We are currently attempting to gain some of the benefits of the feeder layer technique by using medium from rapidly growing stable human cell lines—such as carcinoma of the cervix (Hela), carcinoma of the nasopharynx (KB) and epidermoid carcinoma (H.Ep.)—in static culture or the cytogenerator, reinforcing with glucose, serum, amino acids, and vitamins, freeing it of cells by rapid pressure filtration through 03 Selas filters and using this medium for supporting the growth of unestablished carcinoma cells. No filtration is necessary for medium from the cytogenerator since its fritted glass retains the growing cells, allowing only cell-free medium to pass out as effluate.

Where growth of colonies from a single cell is desired, intimate admixture with living cells themselves, as in the Puck technique, will probably still be necessary. Where a large number of cells are involved or cells are admixed with fibroblasts as in agar plate assays, the use of cell-free medium from rapidly growing cultures of cancer cells may be adequate. One of the important contributions of the Graff cytogenerator may be this possibility of placing the Puck feeder layer technique on a large scale basis or even on a continuous basis, the effluate from culture of rapidly growing human cancer cells after restocking with necessary nutrients as determined by analysis, being used as intake for culture of a second delicate line in a second cytogenerator, or for static culture of human cancer cells or for agar plate tests of a given patient's cancer cells against drugs with and without irradiation of various forms.

As expected, Di Paolo and Moore found that individual members of a specific tumor type varied widely in their reaction to chemicals. Surgeons should no more treat cancer with drugs on an empiric basis than they would treat a Staphylococcus aureus infection on the basis only of results obtained in another part of the country. The therapy program for the individual cancer patient whose tumor has advanced beyond the reach of good surgery must be guided by the results of in vitro tests of the patient's cancer cells exposed to combinations of chemicals

with and without radiation of varying dose and form.

SUMMARY

Perfusion of compounds potentiating radiation therapy increases the antitumor effects of radiation in animals. Compounds were chosen for perfusion to inactivate the sulfhydryl inhibitors of free radical reactions through which therapy by ionizing radiation, such as roentgen-ray and supervoltage therapy, is largely mediated. Chemical binding of sulfhydryl compounds which protect proteins from radiation and are scavengers of free radicals potentiates radiation therapy both in agar plate tests against cancer cells and in animals bearing tumor. The effect is increased by other antimetabolites blocking multiple metabolic and anabolic reactions. For clinical application, large amounts of sulfhydryl inhibitor will be perfused or infused intra-arterially to tumor bed, while the patient is protected by simultaneous intramuscular administration of BAL to antagonize excess sulfhydryl inhibitor.

Rational chemotherapy for the individual cancer patient must be guided by the results of in vitro tests of the patient's cancer cells exposed to combinations of chemicals with and without radiation.

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# TEN YEAR RESULTS OF THE KELLY AND KENNEDY TYPES OF PROCEDURE IN URINARY STRESS INCONTINENCE

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NUMEROUS OPERATIVE TECHNIQUES have been devised to cure urinary stress incontinence in the female, new procedures or modifications of old procedures appearing in the literature from time to time. Recently, Symmonds stressed the need for individualization when considering surgical correction, the extent of the operative procedure being determined by such factors as degree of incontinence, prolapse of the bladder or uterus, displacement of vesical neck, failure of previous surgical procedures, vaginal stenosis and scarring, and an associated surgical procedure necessitating an abdominal incision. With these factors in mind, the gynecologic surgeon is still faced with the problem of deciding which of the numerous abdominal, vaginal, or combined procedures offers the best chance for relief. Usually, the decision is directed by the individual surgeon's personal training, clinical experience, and familiarity with the various procedures. Some surgical procedures, which seem to be anatomically sound, still endure the test of time but appear to offer variable results.

In general, prior to the early 1950's, it was the practice of Mayo Clinic surgeons to employ a Kelly or a Kennedy type of repair for the correction of urinary stress incontinence in the female. In general, the Kelly procedure consists of placing 1 or 2 sutures at the urethrovesical juncture, while the Kennedy procedure consists of plication or imbrication of the "pubocervical fascia" beneath the bladder or bladder neck.

In 1943, Counseller (1) reviewed the Kennedy technique and reported complete restoration of continence in 26 patients whom he had treated; the length of follow-up was not stated. In 1951, in a more extensive study (2), it was reported that plastic operations on the anterior vaginal wall, such as the Kelly and Kennedy types of operation, restored urinary continence in 85 per cent of 578 patients whose progress was noted for at least 6 months.

Review of the literature discloses conflicting reports of success and failure with the Kelly and Kennedy procedures. Miller, utilizing a fascial pleating operation to correct cystocele, noted that preoperatively 43 of 100 patients complained of incontinence and that on follow-up 15 of the 100 patients still experienced incontinence. Graber, without case presentations, reported failure in from 15 to 40 per cent of Kelly procedures. Wharton and Te Linde stated that about 90 per cent of patients with incontinence could be cured by plication of the vesical sphincter with some modification of the Kelly stitch. FitzGibbon reported that incontinence recurred during a 5 year period in 47 per cent of a group of 300 patients treated by 5 surgeons. He also mentioned a presentation at the Royal Society of Medicine in 1946 wherein the estimate of failure ranged from 5 per cent by a gynecologist to 60 per cent by a genitourinary surgeon who claimed that he saw more of the after-results in these cases than did the original surgeons. From these figures, FitzGibbon stated: "It is reasonable to deduce that in this condition the majority of cases seen postoperatively are not allowed sufficient length of time after the operation for a true estimate of the results to be made in this particular respect." Kelly and Dumm, having followed up 20 patients for periods varying from 4 months to 13 years, reported

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a recurrence rate of 20 per cent. Watson reported failure in 12.4 per cent of 105 cases after a follow-up of at least 6 months. Furniss noted 2 failures in 18 Kelly procedures, 11.1 per cent. Te Linde reported 90.3 per cent of 249 patients well, 5 per cent improved, and 3.5 per cent unimproved after the Kennedy operation.

We have appraised the experience and 10 year results achieved at the Mayo Clinic with the Kelly and Kennedy types of repair.

## MATERIALS AND METHODS

From 1 January 1944 through December 1948 at the Mayo Clinic, 522 patients from the United States were treated surgically for primary or recurrent stress incontinence by either a Kelly or Kennedy type of repair; foreign patients were not included because of follow-up difficulties. From case records, personal communications at the time of follow-up examinations at the clinic or hospital, and letters received from physicians and patients, we are able to report on the status of 79.9 per cent of the 522 patients 10 years or more after operation. The 522 patients were grouped according to the following classification:

A. Primary stress incontinence, 472 patients—patients had not been treated surgically for incontinence before coming to the Mayo Clinic.
   1. Primary incontinence as the primary complaint, which resulted in operation, 212 patients.
   2. Primary incontinence as an associated complaint—patients had other gynecologic problems, such as prolapse, bleeding, rectocele, and cystocele, and the operation for incontinence was an accompaniment of repair of other defects, 260 patients.

B. Recurrent incontinence, 50 patients—patients had had surgical treatment previously either at the Mayo Clinic or elsewhere, because of stress incontinence.

The degree of preoperative incontinence was graded in all patients by the attending gynecologist in the following manner: Grade 1, mild—occasional leakage on straining as during coughing or sneezing; grade 2, moderate—leakage on any straining or exertion; grade 3, marked—leakage when patient was erect; and grade 4, complete—leakage when patient was erect or recumbent.

Results were classified according to the following terms: "good," if patient claimed continence at all times; "improved," if occasional leakage occurred on straining but was of no consequence, or if incontinence was markedly decreased; and "failure," if any incontinence remained that was of concern to the patient.

## RESULTS

A primary Kennedy operation was performed on 394 patients. Follow-up after a minimum of 10 years revealed that the operation had been successful in 64.9 per cent, had resulted in improvement in 13.9 per cent, and had failed in 21.2 per cent of 316 traced patients.

A primary Kelly operation was performed on 78 patients with good results in 57.1 per cent, improvement in 7.1 per cent, and failure in 35.8 per cent of 56 traced patients as observed 10 years later.

*Primary incontinence as the primary complaint.* Of 212 patients operated upon primarily because of stress incontinence, 60 had a primary Kelly procedure and 152 had a primary Kennedy procedure. The primary Kelly procedure was followed by good results in 58.5 per cent of 41 traced patients, improvement in 4.9 per cent, and failure in 36.6 per cent. The degree of preoperative incontinence was grade 1 in 7 patients, grade 2 in 37, grade 3 in 12, and grade 4 in 4. Procedures performed at the same time as the Kelly procedure were, for the most part, other than major perineal or gynecologic operations and included ventral herniorrhaphy, cholecystectomy, inguinal herniorrhaphy, cervical cautery, cervical biopsy, dilatation and curettement, and operations for cyst of Bartholin gland or Gartner's duct. Major gynecologic procedures included vaginal hysterectomy in 2 patients, total abdominal hysterectomy in 2, removal of cervical stump in 2, urethral diverticulectomy in 1 patient, repair of en-

terocele in 1, repair of rectocele in 1, and removal of a cyst in the anterior vaginal wall in 1. Thus, it seemed evident that the anterior vaginal wall was relatively undisturbed except for the Kelly procedure. In this sense the operation was a "pure Kelly" procedure, rather than one in which vesical neck stitches were taken in association with repair of a cystocele and which then would more closely resemble a Kennedy type of repair.

The primary Kennedy procedure for primary incontinence was followed by good results as observed 10 years later in 59.3 per cent of 113 traced patients, by improvement in 14.2 per cent, and by failure in 26.5 per cent. The degree of preoperative incontinence was grade 1 in 21, grade 2 in 70, grade 3 in 57, and grade 4 in 4. Gynecologic operations performed at the time of the Kennedy procedure consisted of vaginal hysterectomy in 36 cases, vaginal removal of a cervical stump in 4, repair of enterocele in 4, total abdominal hysterectomy in 4, and partial vaginectomy in 1 patient.

*Primary incontinence as an associated complaint.* Of the 260 patients who were operated upon primarily because of complaints other than stress incontinence but who also had incontinence as one of their complaints, 18 had a primary Kelly procedure and 242 a primary Kennedy procedure.

The primary Kelly procedure was followed by good results in 53.4 per cent of 15 traced patients, improvement in 13.3 per cent, and failure in 33.3 per cent. Although these results appear somewhat more favorable than those observed in the group that had the Kelly procedure for incontinence manifested as the primary complaint, the difference probably is not statistically significant because of the small number of cases involved, and the lack of the more severe degrees of incontinence (Table I) in the group with associated incontinency who had the Kelly procedure.

Associated procedures performed at the time of the Kelly procedure were vaginal hysterectomy in 10 instances, total abdominal hysterectomy in 4, and repair of enterocele in 1 instance.

TABLE I.—DEGREE OF INCONTINENCE—10 YEAR RESULTS

| | *Primary Incontinence* | | *Associated Incontinence* | |
|---|---|---|---|---|
| | *Kennedy* | *Kelly* | *Kennedy* | *Kelly* |
| Grade 1 | | | | |
| Traced | 16 | 3 | 122 | 6 |
| Good | 11 | 3 | 89 | 4 |
| Improved | 2 | 0 | 15 | 0 |
| Failure | 3 | 0 | 18 | 2 |
| Total | 21 | 7 | 141 | 9 |
| Grade 2 | | | | |
| Traced | 50 | 26 | 81 | 9 |
| Good | 31 | 16 | 49 | 4 |
| Improved | 7 | 1 | 13 | 2 |
| Failure | 12 | 9 | 19 | 3 |
| Total | 70 | 37 | 101 | 9 |
| Grade 3 | | | | |
| Traced | 44 | 8 | — | — |
| Good | 24 | 3 | — | — |
| Improved | 6 | 1 | — | — |
| Failure | 14 | 4 | — | — |
| Total | 57 | 12 | — | — |
| Grade 4 | | | | |
| Traced | 3 | 4 | — | — |
| Good | 1 | 2 | — | — |
| Improved | 1 | 0 | — | — |
| Failure | 1 | 2 | — | — |
| Total | 4 | 4 | — | — |

Inquiry as of 1 January 1959.

The primary Kennedy procedure, used in 242 instances in this group, was followed by good results in 68 per cent of 203 traced patients, improvement in 13.8 per cent, and failure in 18.2 per cent. The degree of incontinence was either grade 1, 141 cases, or grade 2, 101 cases (Table I). The higher percentage of good results in this group as compared to the results in the group that had the Kennedy procedure for primary incontinence as the primary complaint should be viewed in respect to the variance in total patients in each group and absence of grade 3 and 4 incontinence in the former group. If the patients with grades 1 and 2 incontinence in the two groups are combined, the Kennedy procedure is then seen to be followed by good results in 66.9 per cent, improvement in 13.8 per cent, and failure in 19.3 per cent.

Associated procedures performed at the time of the Kennedy procedure consisted of vaginal hysterectomy in 213 instances, total

abdominal hysterectomy in 4, vaginal removal of the cervical stump in 14, and repair of enterocele in 15.

*Recurrent incontinence, secondary operations.* Recurrent incontinence necessitated repeated attempts at surgical correction in 50 patients. A Kennedy repair was employed in 37 instances, with good results in 48.5 per cent of 33 traced patients, improvement in 6 per cent, and failure in 45.5 per cent of traced patients. The results of the Kelly operation were equally disappointing. A Kelly repair was employed in 13 instances, with good results in 50 per cent of 12 traced patients, improvement in 16.7 per cent, and failure in 33.3 per cent of traced patients.

A Kennedy procedure was used in the second attempt at surgical correction for 30 of the 37 patients with recurrent stress incontinence. Of the 30 patients, 26 were traced; good results were noted in 15 of the 26, improvement in 2, and failure in 9. The degree of incontinence was grade 1 in 4 patients with good results in 3, grade 2 in 12 with good results in 6, grade 3 in 13 with good results in 6, and grade 4 in 1 patient, an operative failure.

A Kennedy procedure was used in the third attempt at correction in 5 instances, in all of which it failed except in a patient with grade 3 incontinence who after 10 years remains perfectly continent. The incontinence was of grade 3 in 4 of these patients and of grade 4 in 1 patient.

A Kennedy procedure was used in a fourth attempt at surgical correction in 2 patients but the incontinence—grade 2 and 3—persisted in both.

A Kelly procedure was used in the second attempt at surgical correction for 10 of 13 patients with recurrent stress incontinence. Of the 10 patients, 9 were traced: good results were noted in 6, improvement in 1, and failure in 2. A Kelly procedure used in a fourth attempt resulted in failure in 2 of 3 patients; the third patient experienced slight improvement.

These results support the view that if one vaginal plastic operation has failed to cure a patient, the chance is that a second operation of the same type will also fail.

## FACTOR OF SUTURE MATERIAL USED

In an effort to ascertain a possible relationship between the type of suture material used and the degree of success or failure obtained, the results were tabulated in each case in which the type of suture material was definitely stated by the surgeon at the time of operation. Although the groups were small, the beneficial results obtained when a permanent type of suture material of silk or cotton was used seemed to be significantly better than those obtained by the use of chromicized catgut, 62.7 per cent versus 46.9 per cent.

## COMMENT

Probably more Kelly and Kennedy operations have been performed for urinary incontinence than all other operations combined. Except for sporadic attempts at suspension operations, this practice may continue unless adequate long term follow-up studies are made available on the various techniques. We had this in mind at the time this study was begun, and as follow-up letters were returned we were disappointed to learn that early favorable results did not always indicate that late results would be favorable.

To appraise the problem accurately, the same examiner should see each patient before, during, and after operation. Although this could not be done in this study, every attempt was made to gather specific information from the preoperative notes, to learn all technical details of the operation, and to seek unbiased answers in the follow-up letters and examinations. It seems that some patients actually may have been operated on for incontinence of the urgency type and not for true stress incontinence. Likewise, some of the poor postoperative results may be accounted for on the basis of chronic urethritis with its accompanying urgency type of incontinence in patients

now 10 years or more older and with inconstant menopausal changes. These have been classified with the others since the groups, on the basis of actual recorded information, are inseparable.

The impact of 10 years of elapsed time was an indeterminable factor in this study. Lessened muscular tone, increased body weight, and recurrent or new relaxations of the vaginal wall had had time to appear. Taken together, these considerations permit urinary incontinence to be recognized as a dynamic, changing ailment which must be treated as such to achieve maximal success.

Individualization of cases should commence with the initial examination, at which time the gynecologist must accurately differentiate urgency incontinence from stress incontinence; 2 distinctly separate treatments may be required. Similarly, surgical treatment should not always be decided upon at the first visit, since in many cases mild incontinence with little relaxation of the vaginal wall may respond satisfactorily to adequate trial of perineal exercises. Finally, in many cases mild relaxation of the vaginal wall is without symptoms except for rare urinary leakage, and this should simply be recognized for what it is: a small bother, surely not sufficient to warrant surgical attempts at correction.

Individualization of cases should continue at operation, at which time the surgeon not only "raises the vesical neck and tightens the control muscle" but also adequately corrects all other relaxations or protrusions that might ultimately act to tear down the best made repair. Certainly, an adequate physiologic and anatomic reconstruction of the levator mechanism is a minimal requirement. The amount of correction, the type of repair, and the suture materials used are also individualized, as is the recognition, at operation, of the probable inadequacy of a simple vaginal approach or a pure Kelly or Kennedy repair, particularly in respect to incontinence that is recurrent.

Postoperatively, the dynamics of advancing age begin and the clinician should not always say "failure" if leakage commences. With proper anatomic support regained, the physiologic sphincteric mechanism must be started if best results are to ensue and persist. In our practice all patients are instructed, once recovery is well under way, to strengthen the levator muscles and actively continue their use. Should atrophic changes of the vagina and urethra become symptomatic they should be treated adequately. One should treat as well the frequent chronic or granular urethritis that may develop.

Viewed in this way and accompanied by a far broader outlook, surgical treatment of urinary incontinence will become more reliable and offer more lasting relief.

## SUMMARY

A primary Kelly or Kennedy operation was performed on 472 patients whose incontinence was the primary or an associated complaint. Follow-up after a minimum of 10 years revealed that the Kelly procedure had been completely successful in 57.1 per cent of 56 traced patients, while the Kennedy procedure had been completely successful in 64.9 per cent of 316 traced patients.

Recurrent incontinence necessitated surgical correction in 50 patients. A Kennedy repair was employed in 37 instances, with good results 10 years later in 48.5 per cent, improvement in 6 per cent, and failure in 45.5 per cent of traced patients. The results of the Kelly operation were likewise disappointing.

Good results followed use of a permanent type of suture material in 62.7 per cent of cases as compared with good results in 46.9 per cent of cases in which temporary suture material was used; the difference seemed significant.

More accurate preoperative, operative, and postoperative diagnosis is essential in dealing with urinary incontinence, which must be recognized as a dynamic, not a static, condition.

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# A CRITICAL STUDY OF 100 CONSECUTIVE WOUND INFECTIONS

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IN THE PAST, wound infections have been studied in the perspective of their chronologic setting. In this connection Dineen and Pearce (3) reported previously a 10 year review of wound infections from this Center. In the present report 100 consecutive wound infections are considered in order to evaluate various factors—microbiologic, human, and inanimate—which may be of importance in the genesis of wound sepsis in these instances.

One of the mysteries surrounding this problem is the apparent inconsistency of the development of clinical disease after known infection. It is a well known observation that not every wound which becomes contaminated becomes infected. There are obviously many host and parasite factors which come into play in this regard. This study was undertaken to delineate those factors which seem to be of importance in wound infections. Four general areas were considered. These were the etiologic agents, the operation itself, the patient as a host, and the personnel involved. The duration of operation has been considered important in the development of wound infections. It is apparent from this study that such is not the case. However, emergency operations and second operations on the same patient are related very closely to subsequent wound sepsis. The operation preceding the one in which the wound subsequently became infected was found not to be significant.

The patient as a host was studied with particular attention to the presence of underlying disease states and to the use of preoperative antimicrobial drugs, especially neomycin.

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This study was supported in part by Contract No. DA-49-007-MD-689, Research and Development Division, U. S. Army.

## MATERIALS AND METHODS

One hundred consecutive wound infections were studied which occurred in pavilion patients of the Department of Surgery of The New York Hospital-Cornell Medical Center. These occurred not only after general surgery but also after operations in the surgical specialties of urology, plastic, fracture and neurosurgery, ophthalmology, otolaryngology, and pediatric surgery. A wound infection was considered to be present if during the postoperative period, up to 1 month, there was any redness, swelling, induration, or discharge from the wound. In each case a bacteriologic diagnosis was made by aspiration of the wound or by culture of the drainage.

The 100 wound infections occurred during the period of 18 months from 1 June 1958 through 30 November 1960. There were 11,426 operations on the pavilion services in this period. Each operation in which a wound infection appeared was investigated and the following information was obtained.

*Etiologic agent.* In the instance of staphylococci, bacteriophage typing was performed, and the susceptibility to penicillin and novobiocin was determined. These were selected because the sensitivity to penicillin was closely paralleled by erythromycin and tetracycline but was unrelated to novobiocin. This will be the subject of a separate report. With enteric organisms individual isolations were performed to determine each species. Antibiotic sensitivities determined on these are of little significance and are not included.

TABLE I.—ANTIMICROBIAL SUSCEPTIBILITY BY PHAGE TYPE

| | | Penicillin | | Novobiocin | |
|---|---|---|---|---|---|
| *Type* | *Total* | *Sensitive* | *Resistant* | *Sensitive* | *Resistant* |
| Nontypable | 36 | 11 | 25 | 34 | 2 |
| 80–81 | 7 | 0 | 7 | 5 | 2 |
| 80 | 3 | 0 | 3 | 3 | 0 |
| 81 | 1 | 0 | 1 | 1 | 0 |
| Coagulase negative | 1 | 1 | 0 | 1 | 0 |
| Total | 48 | 12 | 36 | 44 | 4 |

TABLE II.—LENGTH OF OPERATION

| | *Staphylococci* | *Enteric* |
|---|---|---|
| Average..... | 3 hours | 3 hours, 10 minutes |
| Longest..... | 6 hours, 10 minutes | 9 hours, 5 minutes |
| Shortest..... | 30 minutes | 40 minutes |
| Average of first operation of the day (infected)..... | 3 hours, 42 minutes | 4 hours, 6 minutes |

*Operation.* Six factors relating to the operation per se were investigated: (1) The duration of each operation was tabulated from the time of the incision to the placement of the last skin suture or drain. (2) The location of the incision which subsequently became infected was noted. These were classified first into general body areas and then, in the case of the abdomen, the types of incision in each quadrant were separately categorized. (3) Second operations after which infection developed were tabulated. In this category were included all instances in which a patient was operated upon a second time during the single hospital admission which did not necessarily mean through the same incision. (4) Emergency operations formed a separate classification. If the wound of this procedure became infected it was so noted (5). In each instance of wound infection the procedure which preceded the operation after which sepsis developed was investigated, except in those instances in which the infection followed the first operation in that particular room on that day. In the study of the "preceding operations" an attempt was made to document any infection or breaks in technique which might possibly have been associated with the subsequent procedure after which sepsis developed. (6) The operations which were performed as the first of the day were listed separately. In this Center it is the custom to perform the more serious operations first. Thus the extent and duration of these would be expected to be greater.

*Patient.* The patient as a host for bacterial infection was evaluated in three categories: (1) An underlying disease was considered to be present only if a documented generalized disease existed. Any disease such as arteriosclerosis was accepted only if severe clinical manifestations existed, e.g., gangrene. (2) The preoperative use of antimicrobial drugs was recorded in each case. Also the specific drugs used in each instance were noted. The postoperative antimicrobial therapy was not included. (3) Trauma or shock was included as a factor in those situations in which severe trauma or clinical shock was definitely demonstrable in the immediate presurgical period.

*Personnel.* The surgeon, assistants, suture nurse, circulating nurse, and anesthesiologists for each operation were noted, and the frequency with which these individuals participated in the operations under study was recorded.

## RESULTS

The infection rate for the 18 month period was 0.87 per cent, 100 infections in 11,426 operations. The etiologic agents recorded were staphylococci in 48 cases; enteric organisms in 49, streptococci (group A) in 3. It is of interest that staphylococci and enteric organisms occurred with almost equal frequency, an observation similar to that made in previous reports from this Center.

In the entire group of infections there were 8 of the enteric group in which a small number of staphylococci were isolated. In the staphylococcal infections there were 3 which were associated with a small number of enteric organisms.

A closer scrutiny of the staphylococci revealed that all except 1 were Staphylococcus aureus, coagulase positive. This was a Staphylococcus albus, coagulase negative. By bacteriophage classification most fell into an untypable category (Table I), and

only 7 were of the 80–81 strain. Of the 48 separate cultures, 36 were penicillin resistant and 44 novobiocin sensitive. Also in Table I the antimicrobial susceptibility by phage type of the 48 strains is shown. The various species of organisms that comprised the enteric group were: Escherichia coli in 20, Proteus vulgaris in 8, Pseudomonas pyocyaneus in 8, enterococci or anaerobic streptococci in 33, Aerobacter aerogenes in 8, fusiformis in 4, Clostridium welchii in 2, corynebacterium in 2, and Bacillus subtilis in 1. It is of interest that Streptococcus fecalis and anaerobic streptococci comprised the most commonly isolated bacteria. Escherichia coli was the next most frequent. In 6 wound infections of this group only 1 species of organism was isolated.

There was no significant difference in the age or sex distribution of those patients with infections as compared to the total group. There was no difference in the duration of the operations in the patients with staphylococcal and enteric infections. The first operation of the day was only about 45 minutes longer in each classification despite the fact that these were the more "serious" operations on the operating schedule (Table II).

The location of the infected wound was most frequently in the abdomen, and the right upper quadrant was involved most commonly (Table III). It is of interest that despite the fact that almost as many procedures—including most operations involving the left half of the colon—were performed in the left lower quadrant as in the right upper, enteric infections occurred three times more frequently in the right upper quadrant. Also it should be noted that of the staphylococcal infections of the lower extremity 7 of 11 were in fracture operations. Of all staphylococcal infections one-sixth occurred in patients with fractures.

Of the 100 wound infections one-third occurred after emergency operations and almost one-quarter after second operations. Over two-thirds of the infections after emergency procedures were caused by enteric organisms (Table IV). The 32 wound infections followed a total of 1,329 emergency procedures, an incidence of 2.4 per cent as compared to the over-all rate of 0.87 per cent. It should be noted also that one-third of the infections occurred after operations which were the first of the day. The etiologic agents were evenly divided in this situation. Although the length of the first operation of the day averaged slightly over 45 minutes longer than the other procedures this fact was not statistically significant.

Twenty-eight per cent of patients received preoperative antimicrobial drugs and most of these were in the group of first operations of the day. Neomycin was the single most frequently used antimicrobial drug (Table V). Streptomycin and penicillin were administered next frequently. Most patients received more than one drug.

Table VI shows that there were 16 patients with a severe underlying disease in whom a staphylococcal infection developed.

TABLE III.—LOCATION OF INFECTED WOUND

| | *Staphylococci* | *Streptococci* | *Enteric* |
|---|---|---|---|
| Abdomen | 26 | 1 | 42 |
| Upper midline | 0 | 0 | 4 |
| Right upper quadrant | 11 | 0 | 18 |
| Left upper quadrant | 4 | 0 | 4 |
| Right lower quadrant | 7 | 1 | 6 |
| Left lower quadrant | 2 | 0 | 6 |
| Hypogastrium | 2 | 0 | 4 |
| Head | 3 | 1 | 1 |
| Chest | 2 | 0 | 0 |
| Lower extremity | 11* | 0 | 3 |
| Upper extremity | 1* | 0 | 0 |
| Low back | 0 | 1 | 2 |
| Neck | 1 | 0 | 0 |
| Flank | 4 | 0 | 1 |
| Totals | 48 | 3 | 49 |

*Staphylococcal infection in open reduction of fractures, 8.

TABLE IV.—OCCURRENCE OF INFECTION

| | *Total* | *Staphylococci* | *Enteric* | *Beta hemolytic streptococcal* |
|---|---|---|---|---|
| No. | 100 | 48 | 49 | 3 |
| In wound of a second operation | 23 | 11 | 12 | 0 |
| Emergency | 32 | 10 | 21 | 1 |
| First operation of day | 33 | 17 | 16 | 0 |
| Preoperative antimicrobials | 28 | 14 | 13 | 1 |

TABLE V.—PREOPERATIVE ANTIMICROBIAL DRUGS USED

| | *Staphylococci* | *Enteric* |
|---|---|---|
| Total | 14 | 13 |
| Neomycin | 5 | 7 |
| Penicillin | 5 | 5 |
| Streptomycin | 7 | 4 |
| Tetracycline | 4 | 1 |
| Chloramphenicol | 2 | 0 |
| Sulfonamides | 4 | 1 |
| Vancomycin | 1 | 0 |

There were 9 patients who similarly suffered enteric infections. The most frequently encountered disease was diabetes mellitus.

Trauma was of significance only in the fracture patients—all of whom obviously suffered severe injury.

There were 2 other patients in whom shock due to hemorrhage was profound in the immediate preoperative period. In 1 of these patients a staphylococcal infection developed and in 1 an enteric.

There was no epidemiologic pattern to the personnel participating in the operations, with reference not only to the staphylococcal but also to the enteric infections. In the 18 month period only 1 person was involved in more than 4 infections of each type. This individual participated in 8 operations following which an enteric infection developed and in 2, a staphylococcal wound sepsis.

## DISCUSSION

Although the basic causes of wound infection remain clouded, certain factors seem to be of unusual importance. A few of the various facets studied in this investigation stand out, that is, emergency operations, second operations, and the preoperative use of antimicrobial drugs. During the 18 month period of this study the over-all wound infection rate was 0.87 per cent whereas the rate in emergency procedures was three times as great—2.4 per cent. There is no ready explanation for this finding since two-thirds of these infections were caused by enteric organisms. Since these organisms presumably come from the patient and not from the environment, one must assume that either the precautions ordinarily taken by standard operating room techniques or the host's defenses are at fault, probably both. For that reason, extreme care should be taken to protect the wound and the areas of potential postoperative sepsis from contamination in these instances.

When a patient has had one operative procedure there is definite evidence that his resistance to bacterial invasion at the time of a second procedure is reduced. This is true on the basis not only of decreased local tissue resistance but also of the lowering of systemic defenses. Almost one-quarter of all the wound infections occurred in second operations. Less than half of these were through the same incision. Consequently when a second operation is performed on a patient within a few days or weeks of a first, a significantly greater chance of infection exists presumably on the basis of decreased host resistance.

The preoperative use of antimicrobial drugs was associated with 28 per cent of the wound infections, mostly in patients who were operated upon as the first operation of the day. Preoperative preparation of the gastrointestinal tract with neomycin was employed in 12 instances of subsequent infection. This apparent increased incidence of sepsis in the presence of an antimicrobial drug is substantiated by experimental studies previously reported by Dineen (2). In essence, these laboratory findings indicated that there was a decrease in host resistance when the bowel flora was reduced or markedly altered. This was presumed to be on the basis of nonspecific resistance and not associated with actual immune reactions.

A second feature of the use of antimicrobial drugs in the preoperative period is the tendency of the agent to remove or destroy susceptible organisms and thus permit the colonization of the nasopharynx, wound, lung, or gastrointestinal tract with resistant, more virulent organisms. For this reason the policy at this Center is to withhold the use of chemotherapeutic agents except when specifically indicated. The prophylactic use

of drugs as advocated by Linton is not subscribed to at this Center.

It is of interest that the distribution of the 100 wound infections into the two major groups was almost equal. Furthermore the incidence of sepsis in second operation, preoperative use of antimicrobial drugs, and first case of the day is almost the same for both groups. Only in the emergency operations is the danger of infection greater from enteric organisms than from staphylococci.

The subclassification of staphylococci was of interest. Thirty-six strains were not typable although the newly isolated phages of Wallmark and Finland will probably be of help in this area. Eleven were penicillin susceptible, an indication that these 36 strains were probably not identical. Penicillin susceptibility was first measured by the disc method and confirmed by the serial tube dilution technique. Only 7 wound infections were caused by the 80–81 strain despite the fact that two nursery outbreaks and several personnel infections due to this strain occurred during this period.

Beta hemolytic streptococcal infections constituted only 3 per cent of all of the infections whereas in the pre-antimicrobial era the number of infections with this organism was much greater and the morbidity and mortality proportionately higher. The reduction in the disease states caused by this organism is probably due in part to the widespread use of penicillin.

In the enteric infections, there was a preponderance of the streptococcal group of organisms, especially enterococci and anaerobic or microaerophylic streptococci. Next in frequency was Escherichia coli. In most instances these infections were multiple in nature, but 6 were caused by single strains.

From Table IV it would appear that wound infection developed more often after the first operation of the day than after later operations. However, they represented the most seriously ill patients and almost four-fifths of these patients had received preoperative antibiotics which may have been the single most important factor in this situation. Also the average duration of these operations was longer. However, duration of operation per se could not be incriminated from this study.

TABLE VI.—UNDERLYING SYSTEMIC DISEASE

| | *Staphylococci* | *Enteric* |
|---|---|---|
| Total | 16 | 9 |
| Diabetes mellitus | 6 | 3 |
| Cirrhosis | 4 | 1 |
| Severe arteriosclerosis | 1 | 3 |
| Malnutrition | 0 | 1 |
| Lymphosarcoma | 1 | 1 |
| Dermatomyositis | 1 | 0 |
| Tuberculosis | 1 | 0 |
| Severe obesity | 1 | 0 |
| Uremia (chronic) | 1 | 0 |

There were no streptococcal infections.

The location of the infected wounds was surprisingly most frequently in the right upper quadrant. The reason for this is not clear.

Underlying disease of a serious nature was present in 25 per cent of the patients. The single most common disease state was diabetes mellitus and second was cirrhosis.

The present concept of infectivity and the manner by which wounds develop sepsis are confused mainly because not every wound which becomes infected with bacteria develops overt clinical disease. Infectivity studied on the experimental level has yielded many interesting but conflicting reports. Goshi and associates have shown that tissue necrosis enhances infection by staphylococci. Conversely, the reduction of bowel flora by neomycin decreases the survival rate of mice infected intravenously with staphylococci. White has shown on a clinical level that individuals with diabetes mellitus have a quantitatively high nasal carriage rate of staphylococci, and in the present report 12.5 per cent of all staphylococcal wound infections occurred in diabetics. Thus there are definite weaknesses in host resistance which can be shown on a clinical as well as on an experimental basis to be associated with a high degree of sepsis.

From a practical standpoint some order may be made from the accumulated data. Emergency and second operations should

be considered as higher risks than others. Although in our present knowledge nothing can be done to alter the apparently weakened state of the host, awareness of the dangers should suggest greater precautions. If antimicrobial drugs are used in an attempt to forestall these infections one runs the risk of preparing the field for bacterial invasion. The biologic vacuum caused by the use of chemotherapeutic agents is most likely to be filled by resistant organisms. The patient with diabetes mellitus or cirrhosis is also a greater risk as regards infection.

It is trite to say that bacteria are not present in the tissues until the area is opened by operation. The bacteria either come from the gastrointestinal or genitourinary tract out to the wound or from the air, skin, or nasopharyngeal organisms in. To prevent the migration or transportation of these organisms strict adherence to technique is paramount as discussed by Beal and Dineen (1). If the gastrointestinal tract is opened or exposed the vulnerable tissues of the wound must be protected. Similarly the skin must be properly prepared as outlined by Mannix and Dineen (6), the operating team adequately masked and gowned, and conversation kept to a minimum. This procedure plus careful and gentle handling of tissues should reduce the danger of contamination and sepsis.

SUMMARY

One hundred consecutive wound infections have been reviewed. Forty-eight were caused by staphylococci, 49 by enteric organisms, and 3 by beta hemolytic streptococci. Thirty-six strains of the staphylococcal group were not typable. The factors which were most frequently associated with wound sepsis in this series were emergency operations, second operations during the same admission, and the preoperative use of antibiotics.

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GENE V. WILLIAMS, M.D.

*Caractacus*

# EDITORIALS

## STASIS ULCER

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STASIS ULCER is a common and often disabling complication of chronic venous insufficiency. It afflicts many thousand persons in the United States every year, a large number of whom are totally incapacitated and suffer severe financial hardship. The numerous modes of treatment and the many failures in the past bear silent witness to the misunderstanding of this problem in general. Too often the treatment has been focused on the local lesion alone while the underlying disturbance of venous function has been overlooked. Effective treatment of the stasis ulcer must be founded on a proper understanding of the basic pathophysiology responsible for the lesion.

The term "stasis ulcer" seems more appropriate than postphlebitic, varicose, gravitational or leg ulcer, since the basic cause of this lesion is stasis or congestion brought on by chronic venous insufficiency. Onset of the ulcer is often precipitated by minor trauma to an area where the skin and subcutaneous tissues are already affected by such stasis changes as edema, pigmentation, dermatitis, and induration. The typical location for the lesion is the "ulcer-bearing area" around the ankle and the distal third of the leg, more commonly over the medial than the lateral aspect.

Stasis results from an abnormally high ambulatory venous pressure in chronic venous insufficiency. The disturbance of venous function is usually caused by extensive and permanent damage from deep thrombophlebitis, such as iliofemoral phlebitis. The veins have suffered severe loss of function from destruction of valves and loss of elasticity, so that the pumping action of the calf muscles is not able to lower the pressure effectively during walking or exercise or to return the venous blood efficiently against gravity. Normal exchange of capillary fluid is disrupted and edema and congestion develop. The ambulatory venous hypertension is not due to residual obstruction or occlusion, as generally thought years ago, for thrombosed veins recanalize soon after the acute phlebitis and remain open even though permanently incompetent. Although venograms will demonstrate patency of the deep veins in the lower extremity, they otherwise add very little information to the knowledge already gained by careful clinical evaluation. Because the damaging effect from iliofemoral phlebitis is so extensive, especially if untreated, the problem of chronic venous insufficiency has so far not been amenable to surgical cure. However, effective measures can be taken to control the permanent venous insufficiency and to prevent stasis complications from it.

The basic principle in the treatment of stasis ulcer is to relieve the stasis; then the lesion will heal. The ulcer will not recur as long as the stasis is kept completely under control. Stasis is relieved very simply by elevation of the lower extremity when at rest, and by adequate elastic support when ambulatory. Most small stasis ulcers will

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heal spontaneously on a regimen of rest in bed, elevation, and moist dressings. For the ambulatory patient with a small lesion, the elastoplast boot is very effective. On the other hand, skin grafting for larger ulcers often shortens the healing time and can be done in conjunction with other indicated operations on the veins.

Stasis from deep venous insufficiency is often intensified by incompetent perforating and superficial veins leading directly into the area of the ulcer and thus increasing the local congestion. Here surgical elimination of all involved incompetent perforators and incompetent superficial veins is often the turning point toward effective control of the entire stasis problem, for direct communications with a faulty deep venous system are interrupted. Such operations can be performed effectively after the initial inflammatory reaction has subsided, even though the ulcer has not healed completely.

Since stasis ulcer is nearly always a complication of deep chronic venous insufficiency, and the disturbance of venous function is therefore permanent, adequate elastic support is usually necessary to prevent recurrence of the lesion. The elastic compression not only aids the pumping action of the calf muscles but also prevents dependent edema and congestion. The type of support must be carefully tailored to the severity of the venous insufficiency and to the daily activities of the patient. Heavy elastic bandages with foam-rubber padding are very effective for severe conditions, while elastic stockings may be sufficient in milder cases. The hollow of the ankle often needs extra padding because of its anatomic configuration. The patient should clearly understand the chronic nature of his healed ulcer, the continued need for proper elastic support, and the advisability of having periodic follow-up examinations.

In summary, effective treatment of stasis ulcer must be founded on a proper understanding of the basic pathophysiology responsible for the lesion. If stasis is relieved, the ulcer will heal. Stasis is controlled by adequate elastic support and by surgical elimination of any incompetent perforators and incompetent superficial veins.

# THE NEBULOUS HYPERTENSION

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FURTHER DISCUSSION on portal hypertension may hold little interest for those who contend that much too much has already been written about it. However, constructive thought regarding the cause of portal hypertension seems to have reached a standstill—largely because of our inability experimentally to reproduce the syndrome. Therefore, it might be well to pause at the present time and speculate on the validity of some of our basic concepts of this disease. For a starter we would like to argue the value of attempting to designate extrahepatic portal obstruction as a cause of portal hypertension.

Extrahepatic portal obstruction is defined as an occlusion of the portal vein, or at times the splenic vein, at any point before entrance into the hilum of the liver. Clinically it may result from congenital obstruction of the vein, a thrombosis due to trauma, stasis, or infection and from pressure from without by tumor or lymph nodes.

Those who hold that the disease is primarily one of portal obstruction contend that it is this obstruction which is the root of the evil, resulting in an obvious and natural hypertension. This theory is tenaciously argued in spite of the fact that such a thesis has never been proved. In fact, quite the reverse seems to be the exact state of affairs, for a persisting portal hypertension cannot be imitated by producing such an obstruction to the portal vein. If, for instance, the vein is ligated at any chosen point along its course in man or animal (in stages) there is an immediate elevation in portal pressure which again returns to normal in a matter of hours or days. Furthermore, this ligation does not produce any other features of the disease such as varices, splenomegaly, or ascites.

If it is not possible to produce portal hypertension by actually reproducing the suspect lesion, certainly this tempting explanation cannot be accepted as its cause. It is far more likely that the obstructed portal vein is the result of the disease itself rather than its cause. Thus a thrombosis, or cavernous transformation, might well occur in a sluggish flow of portal blood or one which at times may be flowing in a reverse direction.

Much the same can be said about some "intrahepatic" portal obstructions. The well recognized and typical patient with "portal hypertension" may occasionally have a normal portal pressure. If it is normal, the pressure itself can in no way be responsible for hypersplenism, varices, or hemorrhage. We have all seen patients with varices without bleeding; bleeding without varices; bleeding, varices, and portal hypertension without cirrhosis or apparent portal obstruction.

Would it not be more realistic to consider increased portal pressure as part of the general symptoms—not its cause? Thus the syndrome would consist of portal hypertension, splenomegaly, hypersplenism, cirrhosis, hepatic necrosis, and ascites. One or more of these components might be absent without altering the general syndrome.

Undoubtedly the term of portal hypertension has and will continue to be extremely useful in denoting a particular clinical entity. However, it should be used with full knowledge that the increased tension is not the actual cause of the disease but is only one of several signs which may be present.

Acceptance of this line of reasoning leaves quite a void in our understanding of the disease. Nevertheless, the "hypertension" explanation has led us into many blind alleys. Maybe the time has come to explore other possibilities such as abnormal amines or steroids which a diseased liver cannot neutralize. Could it be that Guido Banti was right after all and that this syndrome is the result of "humoral" influences?

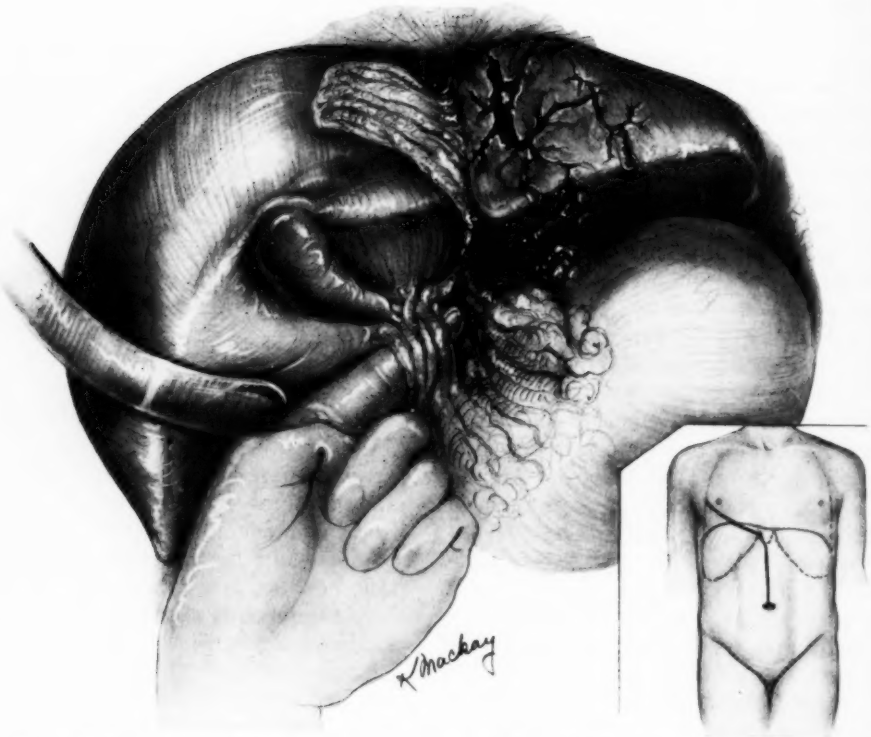


FIG. 1. Drawing showing extent of liver injury and wound of the esophagogastric junction. The inset shows the incision used.

*Emergency Hepatic Lobectomy in Massive Injury of the Liver.* —*William M. Byrd and David K. McAfee.*

# THE SURGEON AT WORK

## EMERGENCY HEPATIC LOBECTOMY IN MASSIVE INJURY OF THE LIVER

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IN DEALING with wounds of the liver, the surgeon is faced with problems of immediate hemorrhage, extravasation of bile into the peritoneal cavity, necrosis, sepsis, and delayed hemorrhage. The inability to control hemorrhage and the complications of the use of absorbable and nonabsorbable gauze packs for control of hemorrhage have been discussed by Madding. As emphasized by Sanders and associates, repair by suture is inefficient and control of hemorrhage is difficult or impossible in the extensively damaged liver. As a consequence the debridement is inadequately performed or entirely neglected. Leaving behind devitalized liver tissue leads to autolysis, sequestration of hepatic tissue, sepsis, secondary hemorrhage, and death. With the present concept of segmental and subsegmental distribution of the hepatic artery and portal vein without significant interarea anastomoses, it seems probable that random debridement of liver tissue will devitalize uninvolved portions of that organ. The importance of necrosis, sequestration of liver tissue, and secondary hemorrhage has been further stressed by Amerson and Blair in a review of 189 cases of hepatic trauma. Postoperative hemorrhage from the hepatic bed, subphrenic abscess, and persistent biliary drainage accounted for 21.7 per cent of their complications. In their patients with liver injury alone, 75 per cent of deaths could be attributed to hemorrhage. Mikesky, Howard, and DeBakey also concluded, after a review of 300 cases, that hemorrhage was the major cause of death in liver injuries. These investigators thought that progress in management of massive trauma to the liver would depend upon refinement in technique of debridement and resection as prerequisites to the control of hemorrhage. Since results of all forms of treatment in massive injury of the liver have been distressingly poor, it seems that hepatic lobectomy would improve results in cases in which the injury is massive but confined to one lobe of the liver.

Resections of lobes of the liver for neoplastic disease with successful outcome have been reported with increasing frequency in recent years. Successful accomplishment of this operation has been beneficially influenced by clarification of certain facts regarding the anatomy of the hepatic vasculature and by refinements of surgical technique. Although partial resections of hepatic lobes have been successful in cases of extensive liver injury, applications of the principles developed in the surgical treatment of hepatic tumors have not been reported.

In a patient who has massive injury to a single lobe, resection should be considered technically feasible if the general condition of the patient permits. The postoperative course should be considerably improved over that of the patient who has a large amount of devitalized liver tissue left. Resection offers the advantages of accurate control of hemorrhage, removal of all involved tissue, and reduction of the possibilities of secondary hemorrhage and abscess formation. As emphasized by Goldsmith and Woodburne, the

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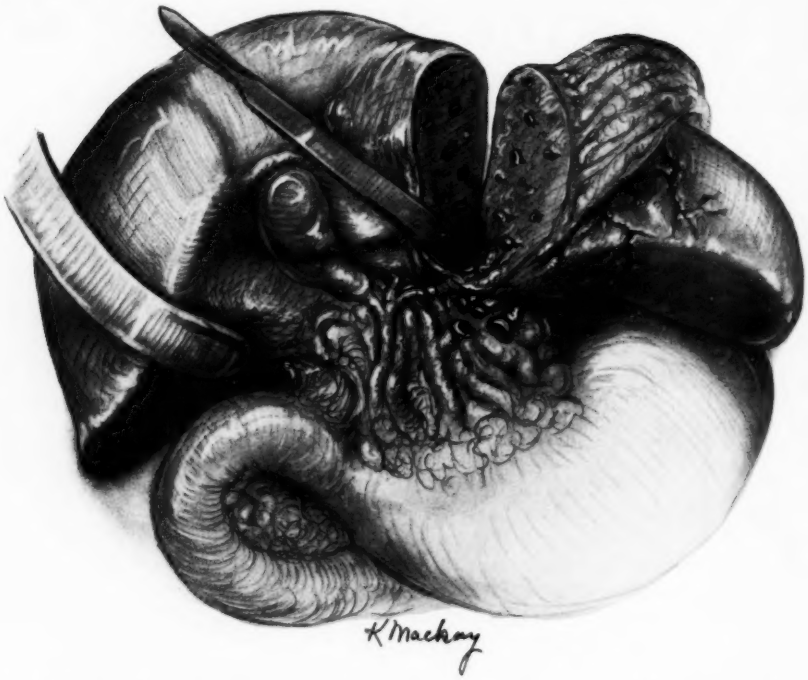


FIG. 2. Drawing illustrating the site and method of resection. All visible vessels and bile ducts ligated with fine silk.

division of the liver into right and left lobes can be made between the terminal venules of the right and left branches of the portal vein within the hepatic parenchyma. The hepatic artery and bile ducts are distributed generally along with the portal vein. The venous drainage does not follow this same pattern. The middle hepatic vein, which drains portions of both the right and left hepatic lobes, lies in the interlobar plane and therefore makes utilization of this division unfeasible for a surgical dissection. Therefore, paralobular planes seem the most satisfactory ones for resection of the liver. This choice is somewhat of a compromise, since it entails leaving a small strip of devitalized liver. The paralobular planes as described by Goldsmith and Woodburne have a sound anatomic basis and provide a useful approach to hepatic lobectomy.

A case in which left hepatic lobectomy seemed indicated was that of a 10 year old girl who was admitted to Grady Memorial Hospital, Atlanta, Georgia 30 minutes after sustaining a high velocity rifle wound of the abdomen. The wound of entrance was in the epigastrium just beneath the tip of the xiphoid process. The bullet was palpable subcutaneously over the right posterior area of the thorax in the eighth intercostal space. Clinically, the patient appeared to be in shock. Dullness and decreased breath sounds were noted over the right lung. The abdomen was distended, nontender, and without rigidity. There was paraplegia with a sensory and motor loss at the level of the tenth dorsal segment. Blood transfusion was started and the patient was taken immediately to the operating room.

A combined thoracoabdominal incision was made. The right pleural space was found to contain 500 cubic centimeters of blood and in the abdominal cavity 1,000 cubic centimeters of blood were found. There was extensive fracture of the left lobe of the liver involving both the visceral and diaphragmatic surfaces and extending into the umbilical fissure. There was also a tangential wound of the esophagogastric junction, perforation of the diaphragm, and moderate intrapulmonary hemorrhage in the lower lobe of the right lung. There was considerable bleeding from the left hepatic vein at its junction with the inferior vena cava as it passed through the diaphragm. The diaphragm was divided from the costal margin to the vena cava. The triangular and coronary ligaments of the left lobe of the liver were divided. This step allowed inferior displacement of the liver and visual-

ization of the site of hemorrhage. Hemorrhage was controlled by placement of a Satinsky clamp and the vein was sutured with a continuous everting No. 5–0 silk suture. The extent of injury of the left hepatic lobe was then evaluated and decision for resection was made (Fig. 1).

On the visceral surface of the liver the left branch of the hepatic artery, the left branch of the portal vein, and the left hepatic duct were individually identified, ligated, and divided. The falciform and round ligaments were reflected and preserved for later reperitonealization of the raw liver surface. The liver was then divided through a plane extending from a point anteriorly approximately 2 centimeters to the left of the gallbladder to the termination of the left hepatic vein and inferiorly through the fissure for the ligamentum venosum. Actual division of the liver was performed bluntly by using the knife handle. The individual vessels and bile ducts were ligated with fine silk as they appeared (Fig. 2). Hemorrhage was minimal during this portion of the procedure. As a precaution against later hemorrhage, the margin of the incision was compressed by means of catgut mattress sutures. The raw liver surface was then covered by suturing the falciform and round ligaments over it. The injury of the esophagogastric junction was confined to the serosa and muscularis and was repaired with fine silk sutures. A Stamm gastrostomy was performed, and the wound was closed with drainage of the pleural cavity and liver bed. A total of 2,200 cubic centimeters of blood was administered during the procedure.

The postoperative course was complicated by accumulation of pleural fluid, requiring two aspirations, and by urinary tract infection of moderate severity. Approximately 3 weeks after injury, the liver function tests were within normal range. The patient has had gradual improvement of the paraplegia with physiotherapy and is now ambulatory with the aid of braces.

The technique described is similar to that advocated by Quattlebaum and Quattlebaum. One deviation from their technique was the placement of compressive catgut sutures along the cut border. This addition was the result of apprehension and uncertainty and probably increased the total amount of devitalized liver. The liver edge was dry before these sutures were placed. Covering with the falciform ligament would have been adequate. It was fortunate that the venous injury in this patient was confined to the left hepatic vein, sparing the middle hepatic vein. Ligation of the bile ducts and hepatic blood vessels was relatively simple in the nondiseased liver of this child. It is anticipated that in the adult with cirrhotic changes this procedure would be much more formidable, if not impossible. The use of the combined thoracoabdominal incision is particularly helpful in providing adequate exposure for this procedure.

## SUMMARY

The rationale, indications, and technique of hepatic lobectomy in the treatment of massive injury of the liver have been discussed. A case has been presented in which left hepatic lobectomy was performed after a gunshot wound. It is postulated that application of the principles discussed will improve results in the management of certain extensive liver injuries when confined to one lobe.

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# A PRACTICAL METHOD OF LEFT RETROGRADE CARDIOANGIOGRAPHY

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IN OUR EXPERIENCE left ventriculography and aortography are the most reliable means of evaluation of aortic and mitral competence. Technical details of such a procedure are presented. More than 250 patients have been examined by this method.

The left ventricle is accessible in three ways by: (1) direct ventricular puncture; (2) left atrial puncture with catheterization through the mitral valve; and (3) retrograde catheterization through the aortic valve. The last technique appears to be the safest and probably will replace the older methods mentioned.

## TECHNIQUE

Under local anesthesia the common femoral artery or, in older arteriosclerotic patients, the right brachial artery is exposed. An arteriotomy is performed and a catheter made of standard 330 polyethylene tubing is inserted. This catheter has a curved tip with 6 side holes and a small end hole (Fig. 1*A*). The catheter is visible on fluoroscopy because it contains a stainless steel spring wire stylet which has a soft resilient tip. This spring stylet is attached to an adapter needle *B* (Fig. 2) through which the catheter can be continuously flushed with heparinized saline solution. Possible air bubbles can be easily detected in the semitransparent nylon extension tube *A* (Fig. 2).

The stylet can be extended through the end hole of the catheter as shown in Figure 1 by pushing the calibrated adapter needle, *B*, shown in Figure 2 into the nylon extension tube *A*. By extending the stylet no more than 5 centimeters the curvature of the catheter is unchanged by the soft wire spring. Further extension of the stylet, however, tends to straighten the catheter (Fig. 3). It is, therefore, possible to give the catheter any degree of curvature, which proved to be extremely valuable in passing the aortic valve.

Under fluoroscopic control the catheter with the wire stylet in place is advanced in retrograde fashion around the aortic arch. Since the wire stylet is not extended beyond the catheter tip the curvature of the catheter is preserved, allowing passage around the aortic arch without entering the brachiocephalic vessels. In the ascending aorta the stylet is extended at least 4 centimeters beyond the catheter tip. It is manipulated through the aortic valve. The extension of the stylet has to be varied according to the degree of tortuosity of the ascending aorta and the position of the aortic valve plane. The passage of the stylet through the valve is best accomplished by moving the catheter up and down and bringing the spring wire stylet in contact with the valve leaflets. This can be recognized readily on fluoroscopy, and in many cases the resilient tip of the stylet will be lifted up by the aortic valve and will suddenly slip through the valve leaflet into the left ventricle. This entrance is readily recognizable by a sudden straightening of the stylet. If the aortic valve cannot be passed in a few minutes, the curvature of the catheter tip is changed by more or less extension of the guide wire. As soon as the tip of the stylet has passed through the valve, it is advanced rapidly into the region of the apex of the left ventricle. A rapid movement of the stylet is advisable since the outflow tract is a sensitive area and numerous premature beats may be induced. The adapter needle *B* (Fig. 2) is then slowly withdrawn, and the catheter is advanced. Ideally the tip of the catheter lies low in the left ven-

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This work was supported by grants from the Minnesota Heart Association, U. S. Public Health Service, National Heart Institute Grant No. 830, and the Minnesota Cardiac Surgery Research Fund.

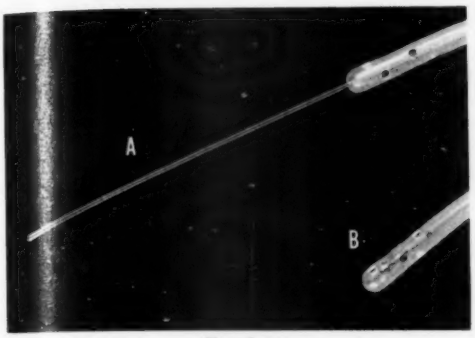



FIG. 1.

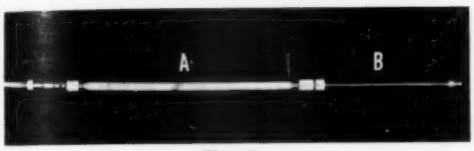



FIG. 2.

FIG. 1. *A*, Ventriculogram catheter with stylet extending through end hole. *B*, Aortogram catheter with end closed.

FIG. 2. Adaptor tube allowing extension of the wire stylet and continuous flushing of system.

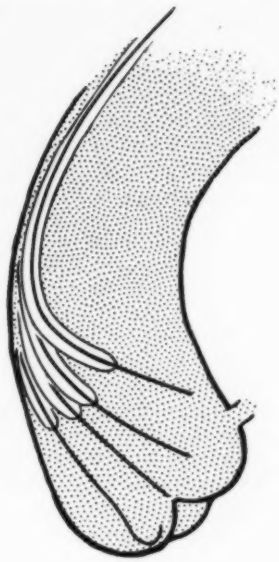


FIG. 3.

FIG. 3. Catheter in ascending aorta. Curvature of tip can be straightened by increasing extension of wire stylet.

tricle near the apex. The extension tube *A* (Fig. 2) is disconnected, and the wire stylet is withdrawn. Pressures are recorded in the left ventricle. Forty to 45 cubic centimeters of 90 per cent hypaque are injected slowly under low pressure by means of a power injector. Since some of the automatic injection devices do not permit a slow rate of delivery of the contrast material, the injection is made through a No. 17 needle approximately 20 centimeters in length. By doing so one is able to extend the injection over at least 2 seconds, in spite of the large bore catheter.

During the first second, 5 roentgenograms are made in each anteroposterior and lateral plane. After this, 3 or 4 roentgenograms per second are made over a period of 5 seconds. A higher rate of speed of filming is used during the first second, since the size of the regurgitating jet may give valuable information about the diameter of the incompetent mitral orifice.

After the injection the catheter is withdrawn slowly into the ascending aorta, and pressures are recorded across the valve. The catheter is removed and replaced by an aortogram catheter of similar design with the tip closed (Fig. 1*B*). By means of the wire stylet this aortogram catheter is positioned under fluoroscopic control so that its tip comes to lie approximately 2 centimeters above the valve plane. A fast injection of 25 to 35 cubic centimeters of contrast medium is made in order to evaluate the competence of the aortic valve.

## INDICATIONS

The procedure is indicated under the following circumstances: (1) evaluation of mitral competence in acquired heart disease; (2) evaluation of mitral competence after operative correction of mitral insufficiency; (3) aortic valvular disease and suspected subvalvular or supravalvular stenosis; (4) small interventricular septal defects with questionable findings by right heart catheterization; (5) balanced interventricular septal defects which cannot be detected by oximetry; (6) patent ductus arteriosus associated with pulmonary insufficiency or with ventricular septal defect; (7) differentiation of aortic pulmonic window from patent ductus arteriosus; (8) demonstration of coarctation of the aorta; (9) demonstration of aortic ring and other vascular anomalies of the arch; (10) evaluation of the left side of the heart in complex congenital cardiac defects; (11) differentiation

between aortic insufficiency and pulmonary insufficiency in mitral heart disease; (12) in all patients with aortic valve disease being considered for surgical treatment by open cardiotomy to evaluate mitral valve competence; (13) in all patients with mitral valve disease being considered for surgical treatment by open cardiotomy to evaluate aortic valve competence.

COMMENTS

The catheter can be introduced either by way of an arteriotomy or percutaneously using Seldinger's technique. This technique is presently under investigation, and so far good results have been obtained. In younger patients or children percutaneous catheterization is preferred. For evaluation of mitral physiology the contrast medium should be ideally introduced through a large catheter, thus minimizing the occurrence of ventricular premature beats which may result in mitral incompetence even in normal patients.

*Choice of artery.* For catheterization the common femoral artery is preferred since it is large and easily punctured and vascular spasm is relatively rare. If the superficial femoral artery is utilized, arterial spasm may be encountered in the younger age group. All studies were performed under a sedative dose of barbiturate.

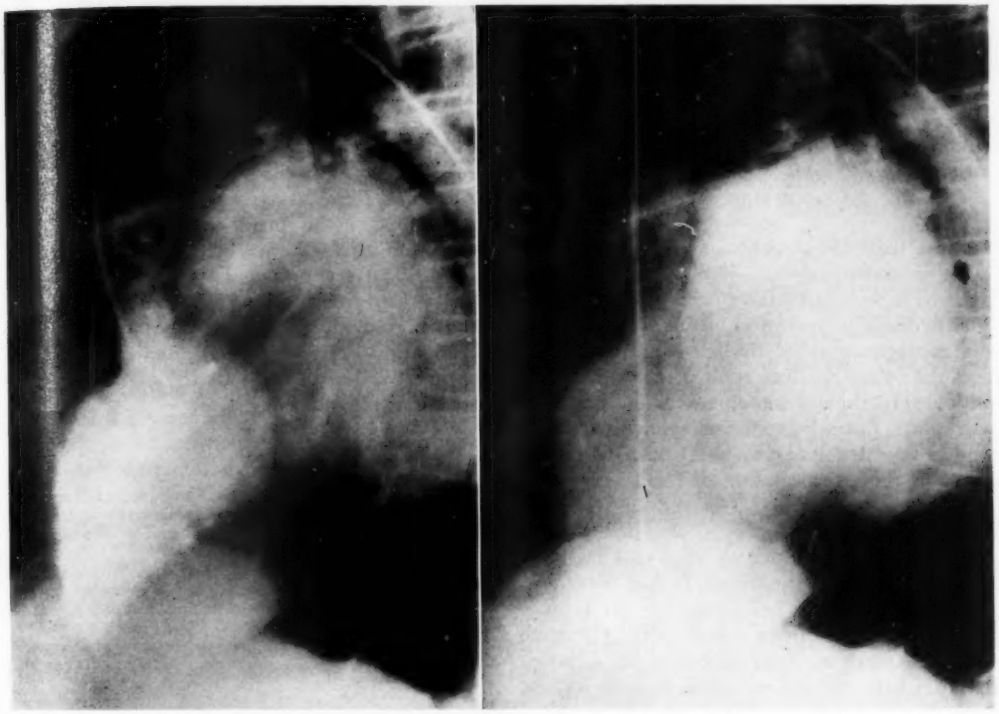
*Choice of catheter.* The catheter should have a wide lumen and a changeable curvature. If the curvature of the catheter cannot be changed, as with regular opaque catheters, the same aortic cusp may be entered in successive passes, and it may be impossible to pass the aortic valve even in normal patients. Regular polyethylene tubing has proved to be an inexpensive, ideal catheter material. The curvature of the catheter can be changed easily by extending the spring wire stylet. Figure 3 demonstrates how different points of the valve plane can be reached by extending or contracting the spring wire stylet.

*Passage through the aortic valve.* In most patients with a normal aortic valve, but aortic insufficiency or mild aortic stenosis, it is surprisingly simple to pass the spring wire through the valve leaflets. Porstmann has shown in animals that it is possible to perforate the aortic valve by exerting pressure with a stiff catheter. This possibility is reduced by the use of the flexible guide wire, and perforation of valve leaflets has not been observed in our personal experience.

In tight aortic stenosis it is sometimes impossible to catheterize the left ventricle through the aortic valve. In such cases it may be necessary to perform a direct needle puncture of the left ventricle and inject the contrast material through a needle. This approach has been used in only 12 patients. The quality of the obtained ventriculograms is considered to be by far inferior to that by the catheter technique. Furthermore, competence of the aortic valve cannot be adequately evaluated.

*Evaluation of mitral competence.* The mitral valve in dogs is incompetent during a run of extrasystoles. Such extrasystoles are produced by a fast and forceful injection with irritation of the endocardium by a jet of contrast material. In these cases there is definite though transient opacification of the left atrium. In animals with artificially created organic mitral insufficiency, however, there is a progressively increasing opacification of the left atrium over several seconds. By application of this knowledge to human studies, it was determined that the contrast material must be added to the left ventricle at a slow rate, preferably without producing extrasystoles, and that film studies must be made over a period of at least 6 seconds. Left ventriculography for evaluation of the mitral valve is a physiologic test and in this sense differs from selective angiocardiography. Enough contrast material is added to the left ventricle over at least 4 consecutive systoles in order to opacify the chamber. If there is mitral incompetence, the left atrium will become progressively opacified. By comparing the degree of opacification of the left atrium with the opacity of the aorta on late films, it is possible to estimate the degree of insufficiency. A grading ranging from 1 to 4 plus proved adequate for practical purposes (Fig. 4).

*Complications.* Two deaths have occurred in association with this procedure. In 1 patient the left atrium was entered accidentally. It was decided to inject 30 cubic centimeters of contrast medium in order to outline this chamber. A perforation of a paper-thin left atrial wall occurred, and the contrast medium collected in the pericardial sac. Cardiac tamponade developed, and an emergency thoracotomy was performed. This patient succumbed the following day. Injection into a markedly dilated left atrium should be avoided.



a b

FIG. 4. Roentgenograms showing true mitral insufficiency with increasing opacification of a markedly enlarged left atrium. a, Beginning of injection. b, Four seconds later.

In a second patient, ventricular fibrillation ensued as soon as the catheter entered the left ventricle. This patient had diabetes with severe coronary atherosclerosis. Review of the preoperative electrocardiogram suggested a recent prior myocardial infarct. On one occasion the left ventricle was perforated and negative pressures were recorded from the pericardial sac. This perforation was associated with chest pain and electrocardiographic changes. The patient improved on bedrest without surgical intervention.

There have been no other serious complications and no neurologic sequelae.

On several occasions the wire stylet entered the left coronary artery. Under the fluoroscope this entrance may be easily confused with a passage through the aortic valve into the left ventricle. The catheter and the stylet cannot be advanced, and arterial pressure tracings are obtained in an area below the aortic valve. In each instance the intracoronary position of the wire stylet was readily recognized and no serious sequelae occurred. In one instance in which the catheter and stylet remained in the coronary artery for a relatively long period of time, the patient complained of mild chest pain and nausea. The electrocardiogram showed bradycardia with an ischemic pattern. After removal of the catheter the symptoms disappeared and the electrocardiogram and the heart rate returned to normal. The catheter was successfully passed through the aortic valve. Left ventriculography and aortography were performed. The electrocardiogram remained normal.

The usual complications associated with an arteriotomy may be encountered. Patients with severe mitral heart disease have a low cardiac output. This definitely increases the possibility of local complications. Adherence to standards of good surgical care are mandatory, and as a result there have been no serious vascular complications in the extremities. Occasionally in arteriosclerotic patients an endarterectomy has

been necessary to restore good pulsatile flow in the femoral artery.

Introduction of a relatively large catheter into the femoral artery in children may be associated with arterial spasm. Under these conditions forceful movement of the catheter may tear the intima.

## RESULTS

More than 250 patients have been examined by this technique (1). Thirty-one of these patients subsequently have been operated upon. The findings at operation were correlated with the roentgenographic findings. The roentgenographic diagnosis was confirmed in all save 2 patients. In these 2 patients a diagnostic error was made, but a subsequent review of the film studies revealed that an actual error had been made in the interpretation of these roentgenograms.

The evaluation of valvular function by this method was found to increase vastly the accuracy of the clinical examinations. It has become a routine essential test before open heart surgery upon either the aortic or mitral valve. The same technique but a faster injection of contrast medium into the left ventricle is used for the more precise diagnosis of certain complex forms of congenital heart disease.

## SUMMARY

Left retrograde cardioangiography is a reliable method for evaluating mitral and aortic incompetence. Technical details for performing this procedure have been outlined. Accurate evaluation of the mitral and aortic valves is of paramount importance in view of the advances in surgical technique. This method has been utilized in more than 250 patients and has been found to be more informative than catheterization of the right side of the heart and catheterization of the left side of the heart by left atrial puncture.

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# A STAINLESS STEEL STRUT FOR CORRECTION OF PECTUS EXCAVATUM

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NUMEROUS TECHNIQUES have been described for correction of a pectus excavatum deformity. There is no doubt that each of these techniques has merit and in the proper hands will produce satisfactory results. Our personal experience has been that the use of a transverse substernal strut offers the most satisfactory long term cosmetic result in repair of the funnel chest deformity. From 1953 to 1958, we employed a homologous rib graft as a strut (1). However, certain inherent disadvantages in this method led us to seek other materials to use as a strut. The disadvantages of rib grafts were twofold: a lack of sufficient variety in size and curvature of the ribs and the possibility of infection after insertion of a homologous bone graft. Removal of a rib strut was necessary in 4 of our patients, and, although it was not technically difficult, the procedure required extensive dissection in order to remove all of the pieces of the degenerated bone.

The successful use of stainless steel prostheses, particularly in the field of orthopedics, led us to devise a strut of this material which could be used for the correction of a pectus excavatum. At this time we were unaware of the work of Paltia and associates in Finland who had also devised a similar strut. The strut described by this group is similar to ours but is somewhat more pointed and is driven through the marrow of the sternum, which we believe to be unnecessary. A technique using multiple metal blades as internal struts has also been described by Rehbein and Wernicke.

It was decided to make the prosthesis straight rather than curved, so that some overcorrection of the depressed sternum would be readily possible. Four different sizes have been made available. The struts are chemically inert and produce minimum tissue reaction. The struts are light and strong but may be bent manually if the necessity arises. The dimensions of the various sized struts are as follows:

| | *Length, mm.* | *Width, mm.* | *Thickness, mm.* |
|---|---|---|---|
| Size A | 190 | 12 | 2 |
| Size B | 150 | 10 | 1.7 |
| Size C | 120 | 10 | 1.5 |
| Size D | 100 | 8 | 1.0 |

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## TECHNIQUE

A bilateral submammary incision is used routinely. The technique of exposure, division of the costal cartilages, and osteotomy of the sternum has been previously described (1). In most instances, to obtain adequate elevation of the sternum, both a horizontal and a vertical osteotomy have been necessary.

After satisfactory mobilization of the depressed portion of the sternum has been accomplished, a strut of the appropriate size is selected. The strut should be long enough so that it will easily bridge the distance from a point lateral to the costochondral junction on one side to a similar point on the other side. We have preferred to use struts which were of sufficient length so that one end would be palpable postoperatively in the subcutaneous tissues. The strut is then passed underneath the sternum in order to hold it in an elevated position. Although we have not had any difficulty, others have indicated that bleeding from the internal mammary vessels occurred in the postoperative period as a result of prolonged contact with the strut. Consequently, it is probably judicious to ligate the internal mammary vessels above and below the point of contact with the prosthesis. A slight amount of overcorrection of the depressed sternum is preferable, since this tends to level out and ultimately gives a more satisfactory cosmetic result.

Each strut has two holes at each end and a series of notches near the end on each side. These notches and holes are utilized for fixation of the strut. Figure-of-eight sutures of chromic

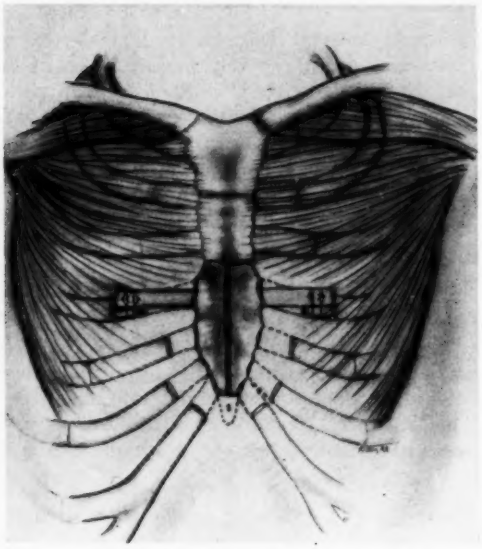

FIG. 1. Schematic illustration of correction after metal strut has been sutured in place. The costal cartilages have been resected and wedge osteotomy of the sternum has been accomplished. In some instances, resection of the third costal cartilage may be necessary.

catgut are passed around the appropriate rib and pectoral muscle and through the holes and notches to anchor the strut in place. This is done at both ends. In no instance has a strut moved after this method of fixation. It is important to place the strut sufficiently high so that it will be under the upper skin flap and will not lie directly beneath the incision. In 1 instance the strut was placed immediately beneath the line of closure of the skin with resultant pressure on the incision. This necessitated early removal of the strut 4 weeks later.

After complete hemostasis has been verified, the wound is closed in the usual manner with adequate drainage of the substernal space. The drain is brought out through a stab wound in the lower midline. Postoperatively, it has been our impression that the patients who have a strut to stabilize the anterior wall of the chest have less pain than those in whom the defect was corrected without the use of a stabilizing device. The patients are usually ambulatory by their third postoperative day and may leave the hospital by the eighth or ninth day subsequent to operation.

Although stainless steel remains quite inert when placed in the body tissues, we have preferred to remove these struts after firm union and stability of the anterior wall of the chest has occurred. This is usually within 8 to 12 weeks after operation. During that time, the tissues form a smooth fibrous casing around the strut, holding it firmly in place. The catgut sutures are absorbed and removal of the strut is quite simple. In no instance have we had an infection associated with the strut, although 2 minor superficial wound infections have occurred in this series. Removal of the prosthesis is facilitated by utilizing a strut which is sufficiently long to be palpable in the subcutaneous tissue.

Removal may be accomplished under local or general anesthesia, the latter being preferable in children. To remove the strut, a 1 centimeter incision is made immediately over the palpable end. The end of the strut is exposed by simply pushing back the subcutaneous fat. One of the holes is then grasped with a towel clip, and on simple, gentle traction the strut slides out quite easily. In some patients, 1 or 2 cubic centimeters of serous fluid have been present within the casing which surrounds the strut. In no instance was this fluid infected and there were no ill effects from its presence. The skin incision is then closed with a simple suture. In none of the patients has there been any change in the cosmetic result which followed removal of the strut.

## RESULTS

The technique which has been described has been used in 18 patients in the past 24 months. The age range was from 3 to 44 years. There have been no deaths in the series and only 2 superficial wound infections. In all instances the strut has been removed without difficulty. The cosmetic results have been good in all patients but 1, the 44 year old adult. This man had an

FIG. 2. Photograph of the stainless steel struts used for correction of pectus excavatum. The smallest size is not shown.

FIG. 3. Postoperative posteroanterior and lateral roentgenograms 1 month after correction of pectus excavatum in a 5 year old male. Note that the strut is slightly to the right of the midline to facilitate subsequent removal.

extremely severe funnel chest deformity with early symptoms of cardiac decompensation. No other cause for the cardiac difficulty could be found. Because of the extensive sternal depression, it was necessary to use two struts in this patient. The convalescence was somewhat prolonged in this patient, and the cosmetic result is unsatisfactory in that there is still some residual sternal depression. However, the patient does not have any further exertional dyspnea or other manifestations of congestive failure since improvement in the defect.

Nearly all of these patients have required some postural training and exercises to correct the slumping of the shoulders and protuberance of the abdomen in addition to surgical correction of the depressed sternum. This training is started as soon as it is possible for the patient to co-operate satisfactorily in the postoperative period.

SUMMARY

A method is described for use of a stainless steel strut to hold the sternum elevated after operative correction of a pectus excavatum deformity. This strut has been used in 18 patients with good cosmetic results in all but 1. The strut is removed 8 to 12 weeks postoperatively after firm union of the chest wall has occurred. No complication have been noted in connection with the use of this prosthesis in this group of patients.

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# TECHNIQUE OF APPLYING AN AUTOGENOUS VEIN PATCH TO AN ARTERIOTOMY

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IN RECENT YEARS there has developed an increasing awareness of the unfavorable influence of narrowing of endarterectomized arterial segments on their ability to remain patent over long periods of time. Senning has introduced an ingenious method of widening the segment at the point of the arteriotomy suture line, the spot at which constriction is most likely to occur. This procedure consists of suturing a patch of autogenous vein, autogenous artery, knitted dacron, or homologous artery into the defect in the arterial wall. Crawford and his associates adopted this same technique.

We have preferred autogenous vein to plastic cloth for the patching material in the hope that it will be incorporated in the new site as living tissue. Since we have found that the thin unsupported vein is rather difficult to handle during the early part of the suturing, a convenient technique has been developed for managing it during this process and is herein described. It consists of mounting the free vein segment to be used as a patch, before it has been incised longitudinally, on a plastic tube, one end of which is inserted into the artery to be patched. The vein is gradually cut away from the stent as the suturing proceeds. Complete control of the vein segment is thus provided which allows suitable tension to be applied during all manipulations.

## TECHNIQUE

Dissect out the selected vein, usually the saphenous, and excise an appropriate length, preferably at a point where the valves are absent, after its branches have been tied. After freeing the lumen of blood by gently flushing it with saline, place the segment into a basin of saline while awaiting its application. At the time the patch is inserted, the vein segment is drawn over a polyethylene tube large enough to fill the lumen of the artery to be patched (Fig. 1).

Incise the vein longitudinally for a distance of slightly more than half the length of the arteriotomy to be closed and insert guy sutures not only at the corners thus created but, also, at the unincised opposite end of the vein to facilitate even traction while suturing. Insert the end of the polyethylene tube into the artery and use circumferential tape to hold it in place. If continuity of blood flow is desired, infuse the proximal end of the tube either by inserting it into another point in the arterial system or by injecting oxygenated blood into it. Allow the end of the tube that is in the artery to communicate with the free lumen by removing the bulldog clamp that closes it off. Suture the middle of the outstretched edge of the vein patch to the corner of the arteriotomy with a single mattress suture (Fig. 2).

Suture the edges of the mid-point of the vein patch to the midpoint of the edges of the arteriotomy on both sides with a single suture. The vein patch is thus arranged in four quadrants to be sutured (Fig. 3).

Trim away the outstretched corner of the vein in one of the upper quadrants in a rounded fashion, and suture the cut edge to the edge of the arteriotomy with a continuous over-and-over everting suture. Similarly, trim and suture the vein in the other upper quadrant. Complete the longitudinal incision in the vein posteriorly, thus freeing it entirely from the polyethylene tube which, however, is to be left in the artery as a stent (Fig. 4).

Stretch out the cut ends of the vein patch with guy sutures as was done at the upper end, and again fix the center of the cut end to the arteriotomy corner with a mattress suture while moving the polyethylene tube to one side so that it can be removed from one of the lower quadrants (Fig. 5).

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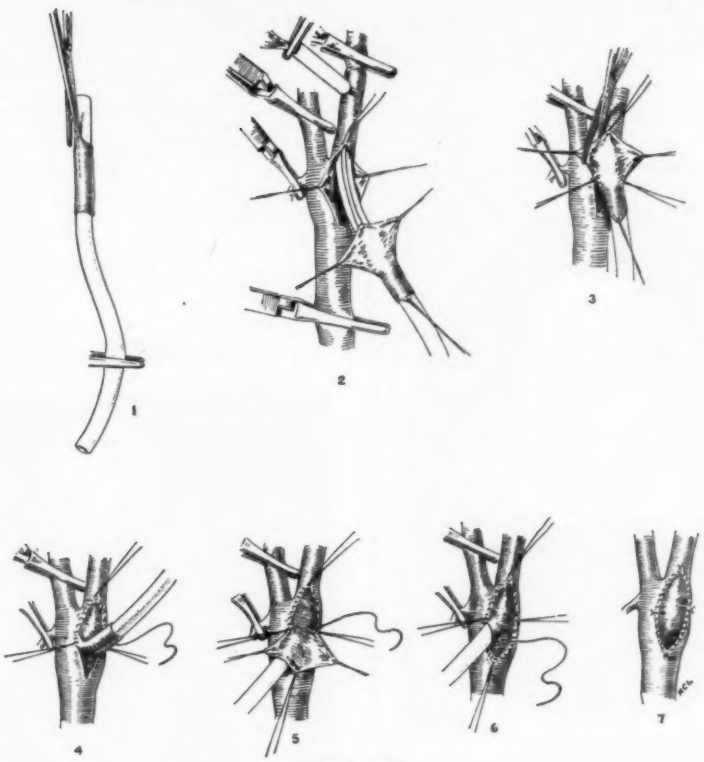
Aided in part by National Institutes of Health Training Grant HTS-5291, Public Health Service.



FIGS. 1 to 7.

Trim the vein corner in the quadrant that does not contain the tube and suture it to the appropriate arteriotomy edge. Then, trim the vein corner in the final quadrant and complete the suturing of this quadrant as far as can be accomplished prior to the removal of the tube (Fig. 6).

Finally, remove the tube and complete the suturing of the final quadrant, being careful to avoid constriction of the patch which in the absence of the stent can easily occur from gathering of bands of adventitia on the vein patch by the suturing process. The clamps are then removed (Fig. 7).

## COMMENT

Trimming of adventitia from the vein patch is performed only close to the edges to be sutured using the finest arterial silk. Mineral oil is applied to it. Trauma to the intima is carefully avoided. The vein patch must be kept continually wet with saline so it will not adhere to the stent.

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FIG. 1.

Fabricius of Hilden
From *De gangraena et sphacelo*, 1617.

FIG. 2.

# *The Book Shelf*

## SURGICAL PATHOLOGY IN THE RENAISSANCE

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IT IS REASONABLE to expect that ideas of regional pathology would follow the prevailing concepts of pathology in general. Such, indeed, was the case in the period of the Renaissance. During the many centuries that the humoral concept of disease was dominant, local lesions were explained on the basis of accumulations in excessive quantities of one or several of the humors in normal or abnormal states. The doctrine was laid down by Galen in his conception of "Tumors Against Nature." These ideas were expanded and embroidered by the writers of later Roman and Arabian periods, and by the time of the Renaissance an elaborate and complex structure had been evolved. An indication of the intricacy of the humoral concept can be gained from the tables taken from the writings of the pre-Renaissance French surgeon, Henri de Mondeville,[1] who possessed a genius for systematic and organized arrangement.

Table I shows the derivation of the humors from the chyle and their normal and abnormal or nonnatural forms, with an indication of the multiplicity of the latter. The term "apostème" was applied by the early French writers to all local lesions thought to be due to excessive accumulation of humors. In Table II the disease entities resulting from accumulations of the various humors are listed singly or in combination, and natural or nonnatural, as the case may be.

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[1] *Chirurgie de Maitre Henri de Mondeville*, translated with notes and a biographic introduction by E. Nicaise. Paris, 1893, p. xlvi.

It is of interest to contrast the attitude toward the galenic theories of two contemporary surgeons, coincidentally bearing the same given name, whose backgrounds and training, however, were quite different and whose beliefs were correspondingly divergent. Hieronymus Fabricius ab Aquapendente (1533–1620) was the leading Italian surgeon of the period bridging the turn of the sixteenth to seventeenth centuries; while Wilhelm Fabricius von Hilden (1560–1624) was his outstanding German counterpart. The dissimilarity of their views can readily be explained on the basis of the difference in their educational preparation.

Fabricius ab Aquapendente (Fig. 1) was born near Orvieto of a good family. He had an excellent preliminary education and was then sent to the University of Padua, at that time the leading educational center of the world. He elected medicine as his career and was fortunate to come under the immediate influence of Fallopius, who was one of the successors of Vesalius to the chairs of anatomy and surgery. It is noteworthy that only in Italy, at that time, was surgery taught in the universities as part of medicine. Fabricius was an exemplary student, both in native intelligence and application; and between him and the gentle, warm-hearted, and brilliant professor a close personal friendship developed as well as an intimate scholastic relationship.

After his graduation, Fabricius had a brilliant career in medicine, with a particular leaning toward surgery. But anatomy was his great love and, eventually, after the early death of Fallo-

TABLE I.—TABLEAU DES HUMEURS D'APRÈS H. DE MONDEVILLE

| | | | |
|---|---|---|---|
| Chyle | Flegme | Flegme naturel | F. aqueux |
| | | | F. mucilagineux |
| | | | F. vitreux |
| | | | F. gypseux |
| | | | F. salé |
| | | Flegme non naturel | F. doux |
| | | | F. pontique, 2 espèces |
| | | | F. acide, 2 espèces |
| | Bile | Bile naturelle | B. citrine |
| | | | B. vitelline |
| | | Bile non naturelle | B. prasine |
| | | | B. aerugineuse |
| | | | B. brûlee, 3 espèces |
| | Sang | naturel | |
| | | non naturel, 5 espèces | |
| | Mélancolie | naturelle | |
| | | non naturelle, 5 espèces | |

TABLE II.—TABLEAU DES APOSTÈMES D'APRÈS H. DE MONDEVILLE

| | | | | |
|---|---|---|---|---|
| Apostèmes | Formés par une hum. naturelle, 4 | | Sang, forme | Phlegmon |
| | | | Bile | Erysipèle |
| | | | Flegme | Oedèmes |
| | | | Mélancolie | Squirrhe |
| | Formés par plusieurs hum. natur., 9 | | Sang et bile, forment | Phlegmon érysipélateux |
| | | | | Erysipèle phlegmoneux |
| | | | Sang et flegme subtil | Apost. intermédiaire |
| | | | Sang et flegme épais | Glandes et noeuds mous |
| | | | Sang, flegme, et mélancolie | Scrofules, glandes |
| | | | Bile et flegme | Apost. insuppurable |
| | | | Flegme épais et mélancolie | Glandes et noeuds durs |
| | | | | Scrofules dures |
| | | | Les 4 humeurs | Carboncle, anthrax |
| | Formés par une hum. non natur., 8 | Non maligne | Sang: Sang subtil et chaud forme | Erysipèle bâtard |
| | | | Sang: Sang épais | Furoncle |
| | | | Flegme: Flegme subtil et mou | Goitre |
| | | | | Tortue |
| | | | Flegme gypseux | Noeuds durs |
| | | Maligne | Bile brûlée: Bile ténue et liquide | Feu persique |
| | | | Bile brûlée: Bile épaisse | Fourmi |
| | | | Mélancolie brûlée | Prune |
| | Formés par plusieurs hum. non natur., 4. | | Les hum. non malignes forment | Glandes |
| | | | | Scrofules dures |
| | | | Les hum. malignes | Miliaire |
| | | | | Herpès |
| | Divers. | | ..... | Apostème cancéreux |
| | | | | Cancer ulcéré |
| | | | | Apostème aqueux |
| | | | | Apostème venteux |
| | | | | Verrues, porreaux |
| | | | | Tumeur simple |

pius, he became one of the succession of brilliant surgeon-anatomists who carried on the tradition of Vesalius in the School of Padua. He was famous as a scientist and lecturer, and for over half a century students flocked from all over Europe to learn from him. Thus was his influence widely disseminated.

The most illustrious of the students to derive knowledge and inspiration from Fabricius ab Aquapendente was William Harvey, and there is no doubt that both of the important contributions made by this English disciple were the outgrowths of lessons derived from this master. Fabricius wrote widely on many phases of hu-

man and comparative anatomy, physiology, and embryology as well as important books in medicine and surgery.

Among these writings were the treatises on the "Valves of the Veins," *De venarum ostiolis*, and the "Fertilization of the Ovum and Generation of the Fetus." Earlier anatomists had observed the valves within the veins, but Fabricius was the first to study them thoroughly and to describe them in detail. He showed that they were present in all the systemic veins and that, irrespective of the vessel examined, the valve openings always faced toward the heart. The obvious conclusion from this observation was that in the veins the blood could flow in only one direction, namely, toward the heart. From this to the next step, of recognition of the circulation of the blood, would appear to be obvious. Certain later writers, indeed, have criticized Fabricius for not taking this next step, a cavil that would appear to be petty and ungenerous in the light of his many monumental discoveries. Nevertheless, it is certain that these demonstrations furnished the platform from which Harvey was able to proceed to his immortal discovery. In a similar fashion, the embryologic investigations of Fabricius led to Harvey's second great contribution, his work on the development of the embryo published in his treatise *De generatione animalium*.

The explanation for Fabricius' failure to achieve the concept of the circulation appears implicit in his thorough indoctrination in the teachings of Galen, an acceptance that brooked no deviation. So closed were the minds of the university-educated physicians that it was beyond their comprehension to differ from or go beyond the dogma into which galenic concepts had become congealed.

The "Surgery" of Fabricius consists of two books, the *Pentateuch* and the *Operations of Surgery*. Of the five sections of the Pentateuch, the first, dealing with "Tumors Against Nature" occupies more than half of the total. Here the galenic concepts, modified to a degree similar to those quoted from Henri de Mondeville, are adhered to with scarcely any deviations. The therapy advocated is logically based on the theory of causation. Thus Fabricius, like the long list of authors who preceded and followed him, perpetuated the humoral ideas of local pathology.

Fabricius von Hilden (Fig. 2), the German counterpart of Fabricius ab Aquapendente, had no university training. He was born in Hilden, a small village in the West of Germany, near Düsseldorf. His father was a judicial clerk and necessarily a man of some education. This Fabricius, too, was to have become a physician, but a series of grave misfortunes intervened. He was but 10 years old when his father died; his stepfather died 3 years later. The boy himself contracted a severe case of bubonic plague which left him bedridden for many months.

Forced by financial stringency to forego university medical education, he turned to surgery as a vocation. He had an excellent practical training under a succession of outstanding master surgeons, and he traveled widely for further learning. He became, as has been stated, the leading German surgeon of his time. He was not itinerant in the usual sense, yet he displayed a considerable restlessness, frequently changing his residence from various German and Swiss locations, with periodic returns to the village of his birth. Further travel was occasioned by his calls in consultation to remote places and the enforced residence away from home for the postoperative care of his surgical patients.

Fabry, as he chose to be called, was a bold and original surgeon. He performed all of the cures and operations of his time and pioneered in several more. He invented numerous instruments and apparatuses for meeting new problems in surgery. Among his many innovations, he was the first to excise axillary lymph node metastases in breast carcinoma. Early in his career he became interested in gangrene and wrote a monograph on the subject. When amputation was necessary, he emphasized the necessity of doing so through healthy tissues above the level of necrosis. He devised a tourniquet for the control of bleeding and is said to have first performed amputation through the thigh.

During his years of very active practice, Fabry collected his *Observationen oder Wahrnehmungen in der Wundartzney*,[2] "Observations or Perceptions in Wound-surgery," and published them in successive series of 100 each, for a total of 600. In addition to these he wrote monographs on gangrene, anatomy, and other subjects. The "Perceptions" include not only detailed case reports with names and addresses of the patients and the names of the physicians and surgeons who were associated with him in

[2]These can be found in his collected works which appeared as: Guihelmus Fabricius Hildanus: *Wund-Artzney*, Frankfurth am Mayn, 1652.

the various cases but also frequent descriptions of autopsy findings. One such is appended herewith. Furthermore, the records include lengthy exchanges of letters between himself and other distinguished physicians and surgeons, in which cases were reported. These, in a way, served the place of the modern medical journals and widened the diffusion of their reciprocal observations.

Fabricius von Hilden, like all surgeons of Germany, France, and England was an empiric. His mind was untrammelled by classic indoctrination. He could see what he looked at and was sufficiently independent of mind to believe what he saw. Thus, we find relatively little of the humors in his writings. Much more was he inclined to find the explanation of diseases in trauma, foreign bodies, parasites, exposure to extremes of temperature, or serious dietary indiscretions. Even in explaining remote complications from local disease or injury, he frequently sought the anatomic pathways for such spread rather than accept the usual influx of humors.

That is not to say that he was unaware of the humoral doctrines or that he rejected them. Rather he placed them in a truer perspective and relegated them to a considerably less important role. His writings show him to be a man of considerable erudition. He wrote in Latin, from which language the books were translated into the vernacular. There are frequent allusions to and quotations from the ancients as well as from more recent authors of his own and other countries.

The following translation of one of his Observations, number 61 of the first 100, is a brief description of the postmortem findings in a patient he had seen during life. It is an example of the clarity of his observation and his perceptive analysis.

THE SIXTY-FIRST OBSERVATION OR PERCEPTION

How an Intestinal Disease Arose from a Hardened Swelling and Cancerous Ulcer in the Region of the Appendix

I have several times visited the son of Theodore on the Koulen in Hilden, who for several years suffered from a persistent and progressive pain in the liver region. When he died of severe intestinal disease, I was called to determine the cause of the preceding pain. When I opened the abdomen, I found that the appendix was shrunken and drawn into the small bowel and so completely filled it that no contents of the upper bowels could be forced into the colon; therefore such pain. When I finally cut the small bowel open and removed the appendix from it, I found the same to be inflamed and swollen throughout. In addition, there was ulcerated hardness present, or more likely a severe cancer in the base of the appendix itself to be seen.

Commentary and Explanation. Various causes are mentioned for the abdominal pain, such as *iliac passion* called by some "Miserere mei" or "Have compassion on me." The primary one is the drawing together and occlusion of the small intestine. And then, to find the cause of this condition, I have opened and examined various corpses, and as the stench was usually most revolting, that one could hardly inspect everything minutely, still I have observed in all that the beginning and cause of this illness is situated about the appendix, that is, in the little pouch which we see at the end of the small intestine and at the beginning of the colon.

For this reason, I believe that the little forward falling door or valve, which the outstanding anatomist and excellent botanist Caspar Bauhin found in the beginning part of the colon, first, as a result of inflammation of the appendix, is so contracted that no feces or excrement can pass through; that then the inflammation so increases that finally the entire small bowel and indeed the surrounding parts become gangrenous and finally are attacked by cold gangrene. I have observed this in all that I have yet autopsied but not only in the above mentioned boy.

Although the precise diagnosis of the specific case may not be evident, his "commentary" provides a lucid description of appendicitis and its sequelae couched in strikingly modern terms.

Thus, in the period of the Renaissance there is a confluence of two streams of thought regarding local or surgical pathology. The classic concept was transmitted by the university-trained physician-surgeons and was merged with the shrewd observations of empiric surgeons whose indoctrination in galenic thought was less rigid and complete. The cumulative volume of the latter contributed greatly to the evolution of pathology as a science and was an effective force in the eventual overthrow of the humoral concept of disease.

# *Reviews of New Books*

**The Operations for Inguinal Hernia** By MARK M. RAVITCH, M.D., and JAMES M. HITZROT, II, M.D. 64 pages, illustrated. $4.00. St. Louis: The C. V. Mosby Co., 1960.

*Reviewed by* C. B. MCVAY

THE MONOGRAPH entitled *The Operations for Inguinal Hernia* by Mark M. Ravitch and James M. Hitzrot is a historical review of the procedures devised and recommended by Bassini, Halsted, Andrews, Ferguson, and Lotheissen, with a final section termed "Johns Hopkins Hernia." For anyone studying the hernia problem and the metamorphosis of present day hernia operations, this well written and accurate treatise should be invaluable.

A discussion of hernia operations in use today will usually produce as many ideas as there are participants as to what constitutes the original Bassini, Ferguson, or Halsted method. As pointed out by the authors, this difference is due in part to the fact that a surgeon's source of information is usually his preceptor and, in part, to the fact that the original authors changed or modified their operations after the original description. For example, in the final Halsted operation, if the relaxing incision is excluded it resembles the Ferguson procedure more than it does the original Halsted method.

The Johns Hopkins hernia operation, a further modification of Halsted's final description of his procedure, is clearly presented. This operation, like the Halsted, the Bassini, the Ferguson, and the infinite variations of these 3 basic procedures, have one feature in common, and that is the use of the inguinal ligament as the anchoring structure. The innovation of imbrication by Andrews was new but did not fundamentally change the basic procedure.

The section on Georg Lotheissen and his use of Cooper's ligament as the anchoring structure includes my opinions upon the principles for the repair of inguinal hernia. The authors conclude this section by agreeing with Leo Zimmerman in that it is not necessary to use Cooper's ligament for a satisfactory hernia repair and that the transition about the femoral vein is difficult and hazardous. Since this is a book review and not an editorial rebuttal, my only comment shall be that the use of Cooper's ligament as the anchoring structure is anatomically correct when the posterior inguinal wall must be repaired. If the only defect is a small indirect hernial sac with slight dilatation of the abdominal inguinal ring all that need be done is to remove the sac and tighten the ring. To add to this simple repair one of the "classic" operations which sutures the conjoined tendon to the inguinal ligament or to tear down a perfectly normal posterior inguinal wall and resuture it to Cooper's ligament is not only superfluous but improperly conceived. The a priori reference is correct as regards surgical experience at that time but not as regards my experience as an anatomist at Northwestern University.

Difference of opinion aside, this is an excellent historical review of the origins of modern hernial surgery and is recommended to all who are interested in the subject.

**The Transplantation of Tissues and Organs.** By MICHAEL F. A. WOODRUFF, M.D., M.S.(Melb.), F.R.C.S., F.R.C.S.E., F.R.A.C.S. 727 pages, 196 illustrations. $25.50. Springfield, Ill.: Charles C Thomas, 1960.

*Reviewed by* THOMAS E. STARZL

THE AUTHOR of *The Transplantation of Tissues and Organs* has attempted to consolidate the available knowledge on this subject into one volume. Emphasis has been placed upon the biologic and scientific importance of recent discoveries, as well as the clinical or potential application of these advances. The collaboration of contributing authors was obtained in only 2 of the 28 chapters.

The first 8 chapters summarize the general biologic features of tissue grafts: autotransplants, homotransplants, and heterotransplants. The mechanisms of and the means of altering immunologic tolerance to foreign grafts are thoroughly discussed. Chapters 9 through 11 outline the broader uses of tissue transplantation as a tool in various branches of biology. The remainder of the text is devoted to a consideration of various tissues and organs. This material is clinically oriented so that most of it bears on the transfer of autologous rather than homologous and heterologous tissue.

The subject matter is organized in a concise and readable manner which will allow easy comprehension for beginners. The thoroughness and accuracy of presentation and the annotation of data with over 4,000 references should make this a standard text of value to all workers in this field.

**Bleeding Syndromes; a Clinical Manual.** By OSCAR D. RATNOFF, M.D. 269 pages, no illustrations. $8.50. Springfield, Ill.: Charles C Thomas, 1960.

*Reviewed by* JAMES W. LINMAN

THE AUTHOR of *Bleeding Syndromes* states: "This book is a compilation of practical information about the clinical picture, pathogenesis, diagnosis, and treatment of hemorrhagic diseases, written for the practicing physician." With this objective, the author discusses current concepts of the physiology of hemostasis and the significance of available diagnostic procedures in the first 2 chapters. Technical details of laboratory tests, however, are not provided. The remainder of the book is comprised of descriptions of the clinical manifestations of virtually all disorders that may be associated, primarily or secondarily, with a hemorrhagic diathesis. Included also are comments on defects in the coagulation mechanism as well as abnormalities of platelets and capillaries.

The variable nomenclature and intricate laboratory techniques used by investigators in this field have created difficulties in communicating the vast amount of recently acquired knowledge. As a result, many physicians have become lost in a plethora of seemingly unrelated experimental and clinical observations. Unfortunately, these obstacles are difficult to surmount. Although this book is intended for the nonspecialist, some readers, relatively unexposed to the complexities of this subject, may not always agree that this goal has been achieved. In addition, certain practitioners confronted with the problem of bleeding may wish that methods for the differentiation of the various hemorrhagic syndromes had been more precisely defined. However, all who are required to evaluate and treat patients with bleeding syndromes should profit from the wealth of clinical data contained in this monograph. There is an extensive, up-to-date bibliography of 731 references.

**Clinical Disorders of the Pulmonary Circulation.** Edited by RAYMOND DALEY, M.A., M.D. Camb., F.R.C.P., JOHN F. GOODWIN, M.D., Lond., F.R.C.P., and ROBERT E. STEINER, M.D.N.U.I., M.R.C.P., D.M.R., F.F.R. 358 pages, 133 illustrations. Boston: Little, Brown & Co., 1960.

*Reviewed by* DONALD FERGUSON

A NEW MONOGRAPH has appeared which approaches cardiovascular problems from the standpoint of the circulation to the lungs. The various chapters in *Clinical Disorders of the Pulmonary Circulation* are written by British authorities, mainly from the Postgraduate Medical School of London. An interesting comment on nomenclature is contributed as a foreword by Paul Wood. Subjects covered in separate chapters are anatomy, physiology, pulmonary function, clinical features of pulmonary hypertension, radiology, pathology, electrocardiography, mitral disease, congenital heart disease, hyaline membrane syndrome, chronic pulmonary disease, vascular obstruction, and pulmonary edema.

In general, the topics are treated competently in a concise and readable style. Practical information about diagnosis and medical treatment is included. The discussions are up-to-date and are backed by extensive, selected reference lists. The weakest chapter is that on anatomy which is too brief and superficial to be of much value. The review of physiology and hemodynamics, on the other hand, is fairly complete. The chapter on pathology, by C. V. Harrison, is comprehensive and well organized. There is little discussion of surgery, beyond a few remarks in the chapter on congenital heart disease. The indications for surgery are usually mentioned, but not in mitral disease.

The chapter that seems to suffer most from the attempt to describe everything from the standpoint of its relation to pulmonary circulation is that on electrocardiography in which there is only a tenuous basis for most of the discussion. The material presented covers a large area of interest for those dealing with cardiopulmonary disease, however, and it is highly recommended to such readers. The typography and illustrations are excellent and there is an adequate index.

**Clinical Gastroenterology.** By F. AVERY JONES, M.D., Hon. M.D., F.R.C.P., and J. W. P. GUMMER, M.S., F.R.C.S. 632 pages, illustrated. $15.50. Springfield, Ill.: Charles C Thomas, 1960.

*Reviewed by* E. CLINTON TEXTER, JR.

A CONCISE, authoritative, up-to-date book on clinical gastroenterology has been lacking from the literature. The present volume, *Clinical Gastroenterology*, represents a serious answer to this need. If it does not satisfy all gastroenterologists, the needs of the internist or surgeon are certainly filled.

The book is based upon the experience of the authors, a gastroenterologist, and a surgeon at Central Middlesex Hospital in Northwest London. Diagnosis and treatment are emphasized. Diseases of the liver and the biliary tract have been omitted because this is intended as a companion to Professor Sheila Sherlock's treatise on this subject. It is well written and pleasingly produced.

The introductory chapter covers the symptoms related to disorders of the alimentary tract. In subsequent chapters, functional disorders of the alimentary tract, motility and its disorders, torsion and volvulus, congenital anomalies, diverticulosis of the alimentary tract, trauma and the alimentary tract, and vascular disorders in relation to the alimentary tract are discussed. The lucid descriptions of torsion, volvulus, and congenital anomalies are enhanced by simple line drawings.

The last two-thirds of the contents are devoted to a systematic description of various disease entities: benign and malignant tumors, hiatal hernia, peptic ulcer, Crohn's disease, and proctocolitis. The descriptions of the pathophysiology and the treatment of hiatal hernia and peptic ulcer are of particular interest.

Steatorrhea and gastrointestinal hemorrhage are discussed. Diseases of the pancreas, the peritoneum, and miscellaneous disorders, which are otherwise unclassifiable, are discussed briefly. The final chapter deals with diagnostic techniques.

The authors speak from a wealth of personal experience. This book is highly recommended to all who are interested in this rapidly evolving field.

**Biology of Pyelonephritis.** Edited by EDWARD L. QUINN, M.D., F.A.C.P., and EDWARD H. KASS, M.D., Ph.D., M.A. (hon.), F.A.C.P. 696 pages, illustrated. $18.00. Boston: Little, Brown & Co., 1960.

*Reviewed by* A. P. HARRIS

WITH THE PUBLICATION of the proceedings of the Henry Ford Hospital International Symposium on *Biology of Pyelonephritis*, a valuable reference text has been added to the medical literature concerning this common disease process. In order to make this possible, Editors Quinn and Kass, along with their program committee, were able to assemble the finest conceivable array of talent for this effort, each being a widely recognized authority in his particular realm of interest.

Although this material represents an up-to-date summarization of clinical and laboratory research presently being conducted regarding pyelonephritis, it

is apparent that far more questions were posed than there were answers given. However, as Oliver points out, this should be construed as progress since the question asked must have the characteristics of testability and confirmability for the answer to be meaningful.

Little more than the generally accepted belief that pyelonephritis is a serious disease received unanimous support in this symposium. Basic features, such as pathogenesis, natural history of the chronic form of the disease, its histologic appearance, and even its incidence, receive multiple descriptions and interpretations.

It becomes abundantly clear that the renal morphologists and functionalists are much nearer the desired hand-joining stage of common effort and understanding of this problem than are the clinical disciplines. The schism between the internist and urologist, if anything, has deepened. The interpretation of experimental data plays no small part in this controversy. Some of this disagreement stems from the misleading equivocation of the terms bacteriuria and pyelonephritis. More fuel is added in the discussion of pyelonephritis induced experimentally in rats by the intravesical injection of bacteria. Clinical inferences are drawn but no allusion is made to the knowledge of the fact that vesicoureteral reflux of urine occurs freely and normally in this animal and only pathologically in the human. The final conflagration erupts in the summation when the time worn, and by many, honored, dogma "obstruction begets infection" comes under attack. There is even a suggestion that the reverse may be the case. So the blaze heightens and dims the outlook for an early solution.

Highlighting the symposium is the presentation in fascinating detail of the remarkable recent achievements in linking renal structure and function utilizing microdissection, micropuncture, cytochemistry, and electron microscopic techniques. Though much of this material is concerned with the normal kidney it is easy to see that the further perfection of these procedures will contribute quite considerably to the final understanding of the disease process in question.

Professor Oliver's comments are a particular delight, with an occasional barb thrown hither or yon. One of the more descriptive ones refers to the technique of stop flow analysis as an elaborate two glass test.

The recordings of this symposium will be of considerable value for some time to come as a reminder not only of the massiveness of the accumulated effort which has already transpired but also of the limitless nature of that which lies ahead.

Meanwhile pyelonephritis remains an ill defined, inexplicable event in the twilight zone of understanding.

**Principles of Surgical Practice.** By EMANUEL MARCUS, M.D., Ph.D., and LEO M. ZIMMERMAN, M.D. 430 pages, 58 illustrations. $12.50. New York, Toronto, and London: McGraw-Hill Book Co., Inc., The Blakiston Division, 1960.

*Reviewed by* JOHN H. SCHNEEWIND

THE PREFACE to this volume is of more than ordinary interest as it not only clearly states the purpose for which it was written but touches upon the increasing difficulty confronting medical educators because of the rapid advances in knowledge in all branches of medicine. The authors believe that the "elimination of unessential material and the attempt to substitute education for technical training" would help to reduce the time required to prepare the physician for the practice of medicine. They believe that a thorough grounding in the underlying principles should be substituted for the memorizing of a great many facts. *Principles of Surgical Practice* was prepared to serve as an introductory course and a framework upon which the facts to be learned later in wards and laboratories could be based. It is devoted to outlining the principles of alterations in anatomy and physiology rather than to a description of syndromes and therapeutic methods.

The 36 chapters contain the basic principles of general surgery and include consideration of inflammation and wound healing, surgical microbiology and the management of infection, wounds, and shock.

In Chapter 2, for example, there is a discussion of infections of the hand and tendons which states the basic principles clearly and completely. In the chapter on "Management of Wounds" the basic principles in the care of hand injuries as well as wounds elsewhere in the body have been considered.

There are the inevitable minor deviations and controversial points, such as the question of labeling tendons for the purpose of easier identification for future procedures. Similarly, one would emphasize the positioning of the hand in flexion after the repair of flexor tendons rather than in the position of function.

The outline at the beginning of each chapter as well as the summary of contents at the end will be of particular value to the student. The volume is handsomely prepared and is very easy to read and handle. The 76 black and white illustrations are pertinent to the discussions and one, double-page spread of attractive color illustrations has been included.

It would seem that the authors have achieved their purpose admirably in presenting a great many principles basic to an introductory course in general surgery, and that, in general, students will welcome this publication. Those who desire or are required to obtain more details about the various subjects may refer to the suggested readings listed at the end of each chapter or to the other surgical references.

**Atlas of Anatomy and Surgical Approaches in Orthopaedic Surgery. The Lower Extremity:** Vol. II. By RODOLFO COSENTINO, M.D. 264 pages, 139 illustrations. $14.00. Springfield, Ill.: Charles C Thomas, 1960.

*Reviewed by* J. WILLIAM HILLMAN

THIS SECOND VOLUME in the series of two on the subject of the anatomy and surgical approaches in orthopedic surgery has as much merit as was given to the initial volume. This type of publication is of great value because the dissections were carried out meticulously and the photographic technique of them is superb. The reproductions of the dissections actually show what each former medical student saw in the anatomic specimens which he himself prepared.

The text matter is sparse and well chosen. Those who intend to use this material for study and review should have both volumes.

**The American Academy of Orthopaedic Surgeons; Instructional Course Lectures.** Edited by FRED C. REYNOLDS, M.D. Vol. XVII. 406 pages, 358 illustrations. $18.50. St. Louis: The C. V. Mosby Co., 1960.

*Reviewed by* LEONARD F. PELTIER

THE INSTRUCTIONAL COURSE LECTURES of the American Academy of Orthopaedic Surgeons for 1960 are presented in the same attractive format that was adopted last year. They consist of a series of papers arranged in 5 main groups: fractures, bone graft surgery, children's orthopedics, athletic injuries, and miscellaneous. The papers are brief and informative, and the illustrations are of excellent quality. It appears that the new editor and the publisher are maintaining higher standards of excellence. This volume could be read with profit by anyone interested in the treatment of fractures or other injuries.

**Hospital Infection; Causes and Prevention.** By R. E. O. WILLIAMS, M.D., M.R.C.P., R. BLOWERS, M.D., L. P. GARROD, M.D., F.R.C.P., and R. A. SHOOTER, M.D. 299 pages, 12 illustrations. $7.50. Chicago: The Year Book Publishers, Inc., 1960.

*Reviewed by* CARL W. WALTER

FOUR EXPERIENCED INVESTIGATORS collaborated in presenting the current knowledge of hospital cross infections in this coherent, well proportioned, comprehensive monograph that compels admiration for their maturity and perspective.

A forthright appraisal of the incidence of hospital cross infection and its economic import outlines the scope and urgency of the subject. The epidemiology of types of infection is next related to the various categories of hospital care, as well as etiologic agent. Included in this section is one of the few discussions of gram-negative infections to be found in the literature.

The material on the administrative responsibility for control of infections provides a refreshing introduction to that half of the text which deals with the practical aspects of control.

The organizational context and the responsibilities of the infection control officer are given in detail. Many physicians struggling with such an assignment will find this helpful.

The chapters reviewing structure, equipment, and practices in hospitals as they relate to the spread of infection or its reverse, control, must be read with the recognition that, while the ecology of cross infection is the same the world over, the design and function of British hospitals differ sufficiently from American that the observations and recommendations presented so convincingly are not amenable to extrapolation. Rather, these chapters are an excellent check list by which to review hospital hygiene item by item as a survey or re-evaluation of current practices on the American scene.

Anyone who has worked on problems of hospital infection will appreciate this book enormously. It should be studied by administrators and nurses responsible for the institutional care of patients. Its reading will provoke discussion and settle controversy among the profession. Surgeons and obstetricians, in particular, should be indebted to the authors for a job well done.

**Textbook of Medical Physiology.** By ARTHUR C. GUYTON, M.D. 2nd ed. 1154 pages, 774 illustrations. $15.50. Philadelphia and London: W. B. Saunders Co., 1961.

*Reviewed by* GILBERT S. CAMPBELL

THIS textbook on medical physiology by Arthur C. Guyton is a single author book with 1154 pages. He states that interrelationships of functions of the different organ systems of the body and the presentation of physiology as a functional rather than a descriptive subject can be more fully realized in a single than a multiple contributor book.

Its 82 chapters are grouped in 13 subject parts, and throughout repetition, so often encountered in multiple contributor books, has been avoided by accurate cross references to other areas of the text. The first part deals with the cell and its function, and the final chapter on "Nuclear Physics and X-rays" includes diagrams of the cyclotron, the atomic pile, and instruments for the detection of radioactivity.

Some surgeons would disagree with the pessimistic evaluation of the role of splenectomy in clinical medicine, with the surgical treatment of cardiovascular defects, with the statement that artificial pneumothorax is a very common clinical procedure; however, these and other insignificant points of difference are submerged by the excellence and organization of the author's broad study into all fields of physiology. Obviously, in any single author publication, some areas of the subject are more extensively and, perhaps, more lucidly reported upon than others, but the successful efforts in the development of this completely revised, second edition of his *Textbook of Medical Physiology* are commendable.

**Clinical Use of Radioisotopes.** Edited by THEODORE FIELDS, M.S., F.A.C.R. (Assoc.), and LINDON SEED, M.D. 2nd ed. 462 pages, 77 illustrations. $10.50. Chicago: Year Book Publishers, Inc., 1961.

*Reviewed by* ROBERT M. DOWBEN

THIS UNPRETENTIOUS, "do-it-yourself" compendium of isotope techniques in clinical medicine will be of considerable use to the laboratory technician and to the house officer and physician who plan doing casual work with radioisotopes. It spells out the routine clinical diagnostic tests of thyroid function, blood volume, red cell survival, cardiovascular studies, tests using cyanocobalamine, and tests of gastrointestinal function. Treatment of thyrotoxicosis and thyroid cancer with radioiodine, of blood diseases with radiophosphorous, and intracavitary therapy are discussed. Considerable attention is devoted to the pragmatic details of planning and operating a radioisotope labo-

ratory, and the attendant details of radiation safety. The sophisticated worker and the physician with a continuing responsibility in diagnosis and treatment who are working with radioisotopes will want much more detail than has been given. The carefully chosen bibliography will be helpful in this connection. Much of the information in this volume can be obtained free of charge from equipment manufacturers and distributors of radioisotopes.

**Cleft Lip and Palate Rehabilitation.** By WILLIAM H. OLIN, D.D.S., M.S., and DUANE C. SPRIESTERSBACH, Ph.D. 190 pages, 85 illustrations. $9.00. Springfield, Ill.: Charles C Thomas, 1960.

*Reviewed by* ORION H. STUTEVILLE

THIS MONOGRAPH of 7 chapters, 190 pages, and 85 illustrations concerns the problems of cleft lip and palate. It starts out with a brief historical review and a report of the incidences of congenital clefts in live births in various countries.

Embryology theories are mentioned, etiology is discussed, and a classification is given. Chapter II is devoted to the feeding problem in early life. Chapter III covers, very briefly, the surgery of cleft lip and palate, both early and secondary procedures. In Chapter IV general dental problems are discussed; in Chapter V speech in its normal development and the difficulty brought about by defects in the various structures necessary for normal speech are the topics presented; in Chapter VI, orthodontic problems are given with illustrations and case reports; in Chapter VII the prosthetic phase of rehabilitation is presented thoroughly giving the technique for constructing the speech appliance with actual case reports.

This monograph should be useful to those interested in the general problem of cleft lip and palate but is not complete enough in any one particular phase of the problem to serve as a text or reference source.

**Good English for Medical Writers.** By FFRANGCON ROBERTS, M.A., M.D., F.F.R. 173 pages, no illustrations. $4.50. Springfield, Ill.: Charles C Thomas, 1960.

*Reviewed by* F. JOHN LEWIS

THIS NEW GUIDE BOOK on medical writing will be welcomed by any physician writer who can find time to try and improve his skill. All should try, for errors abound. The common mistakes and their remedies are clearly described by Ffrangcon Roberts in an absorbing manner which avoids what he calls the worst literary crime—dullness.

It is similar in purpose and scope to Fishbein's book on medical writing and the more recent book by Hewitt, but it is apparently the first one from England. Thus, it is interesting and somewhat disappointing to see in examples taken from the British medical journals that our colleagues have much the same troubles that we have. At their best, as in this book, they may still outdo us.

Roberts finds indirect expression the commonest fault in medical writing but describes many others such as a preference for the passive voice and a tendency to grandiloquence which commonly weaken medical writing. Examples and their corrected versions are used effectively throughout in a profusion that could intimidate the amateur writer. Perhaps the surgeon writer will find some comfort in learning that the most poorly written articles are not on surgery but on medical education.

Though all 16 chapters are valuable, the first two and the chapter on "Clinical Descriptions" were particularly enjoyable.

**Anaesthetic Accidents.** By V. KEATING, M.B., B.Ch., D.A., F.F.A.R.C.S. 2nd ed. 282 pages, 14 illustrations. $5.50. Chicago: The Year Book Publishers, Inc., 1961.

*Reviewed by* EARL A. SCHULTZ

THIS SECOND EDITION of *Anaesthetic Accidents* is a short, eminently readable, well printed edition of the first publication issued in 1956. While its form and style are good, its content should not be given unqualified approbation. Not unlike the little girl, when it is good it is very, very good, but when it is bad—though not horrid—it is at least annoying. In general, the handling of the incidence and diagnosis of the various complications which occur during anesthesia is excellent while the discussion of the therapy is less thorough. For example, neither the chest thump or external cardiac massage is discussed in an otherwise competent section on cardiac arrest. Some errors of omission, in part, perhaps were due to the inevitable lag of time between completion of the manuscript and publication, but this obligatory latent period does not account for the omission of the use of position in the treatment of air embolism or of carotid and/or ocular pressure as a diagnostic and therapeutic maneuver in paroxysmal tachycardia.

There are, most certainly, bright spots in the volume. The author's attitude toward anesthetic fires and explosions is both laudable and realistic, his observations on the deficiencies of gas machines merit attention, and his suggested outline for the management of postoperative respiratory obstruction should be mandatory reading for personnel dealing with the patient emerging from anesthesia.

Since the book is an English publication, the British medical bibliographic notation has been followed. I have no disagreement with author alphabetization of source material at the end of each chapter, but the absence of a specific title for each reference limits the reader who may seek further information and obligates him to read more papers than necessary. To be sure, we are not completely free of these bibliographic sins in this country, but this type of arrangement does limit its utility. The index is inadequate and actually does the book an injustice. Much more information has been included than a casual glance at the index would indicate.

## BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selection will be made for review in the interests of our readers and as space permits.

CHEMISTRY OF DIGESTIVE DISEASES. By John R. Gamble, M.D., and Dwight L. Wilbur, M.D. 115 pages, 2 illustrations. $4.50. Springfield, Ill.: Charles C Thomas, 1961.

DISEASES OF THE INTERVERTEBRAL DISC AND ITS SURROUNDING TISSUES. By Reuben Rabinovitch, B.A., M.Sc., M.D. 137 pages, 78 illustrations. $8.50. Springfield, Ill.: Charles C Thomas, 1961.

ROENTGENOLOGY OF INTRACRANIAL MENINGIOMAS. By Sidney P. Taub, M.D. 222 pages, 128 illustrations. $14.00. Springfield, Ill.: Charles C Thomas, 1961.

CLINICAL DISTURBANCES OF RENAL FUNCTION. By Abraham G. White, M.D., F.A.C.P. 439 pages, 83 illustrations. $10.50. Philadelphia and London: W. B. Saunders Co., 1961.

ISTOPATOLOGIA GINECOLOGICA E GRAVIDICO-CORIALE. By G. B. Candiani and G. Remotti. 274 pages, illustrated. Milano, Italy: Farmitalia, 1961.

DIAGNOSTIC CYTOLOGY AND ITS HISTOPATHOLOGIC BASES. By Leopold G. Koss, M.D., with Grace R. Durfee, B.S. 360 pages, 776 illustrations. $16.50. Philadelphia and Montreal: J. B. Lippincott Co., 1961.

STAFILOCOCCIE DI INTERESSE CHIRURGICO. By G. Fojanini, A. Picciocchi, and E. Fedele. 107 pages, illustrated. Rome: Edizioni Mediche e Scientifiche, 1960.

DIE PRAEOPERATIVE ROENTGENBESTRAHLUNG DES MAMMAKARZINOMAS. By E. Muntean. 106 pages, 9 illustrations. $4.40. Stuttgart: Georg Thieme Verlag, 1961.

CHIRURGIA DELLE ARTERIE MESENTERICHE. By Luigi Imperati and Tommaso Tommaseo. 192 pages, 116 illustrations. Rome: Edizioni Mediche e Scientifiche, 1960.

SYNOVIAL JOINTS; THEIR STRUCTURE AND MECHANICS. By C. H. Barnett, M.A., M.B., F.R.C.S., D. V. Davies, M.A., M.B., B.S., and M. A. MacConail, M.B., D.Sc., M.R.I.A. 290 pages, 60 illustrations. $11.50. Springfield, Ill.: Charles C Thomas, 1961.

ILLUSTRATIONS OF THE NERVOUS SYSTEM; ATLAS III. By Louis Hausman, M.D. 168 pages, 155 illustrations. $9.50. Springfield, Ill.: Charles C Thomas, 1961.

CONTRIBUTIONS TO OBSTETRICS AND GYNAECOLOGY. By V. N. Shirodkar, M.D.(Bombay), F.R.C.S.(Eng.), F.A.C.S. 150 pages, 196 illustrations. $8.50. Edinburgh and London: E. & S. Livingstone Ltd., 1960; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

BLOOD PLATELETS. Edited by Shirley A. Johnson, Ph.D., Raymond W. Monto, M.D., John W. Rebuck, M.D., Ph.D., and Robert C. Horn, Jr., M.D. Henry Ford Hospital International Symposium. 700 pages, illustrated. $18.50. Boston: Little, Brown & Co., 1961.

DISEASE AND INJURY. Edited by Leopold Brahdy, M.D. 464 pages, 6 illustrations. $12.50. Philadelphia and Montreal: J. B. Lippincott Co., 1961.

SYMPTOM DIAGNOSIS. By Wallace Mason Yater, A.B., M.D., M.S.(Med.), F.A.C.P., and William Francis Oliver, B.S., M.D., F.A.C.P. 5th ed. 977 pages, no illustrations. $15.00. New York: Appleton-Century-Crofts, Inc., 1961.

STERILITY; OFFICE MANAGEMENT OF THE INFERTILE COUPLE. Edited by Edward T. Tyler, M.D. 399 pages, illustrated. $12.50. New York, Toronto, and London: McGraw-Hill Book Co., Inc., 1961.

A TEXTBOOK FOR MIDWIVES. By Margaret F. Myles, S.R.N., S.C.M., H.V.Cert., Sister Tutor Cert., M.T.D. Foreword by Jean P. Ferlie. 4th ed. 757 pages, 389 illustrations. $8.50. Edinburgh and London: E. & S. Livingstone Ltd., 1961; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

# AMERICAN COLLEGE OF SURGEONS

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## *PRELIMINARY PLANS FOR THE 47TH CLINICAL CONGRESS THE CONRAD HILTON HOTEL, CHICAGO, ILLINOIS 2 THROUGH 6 OCTOBER 1961*

IN THE JUNE ISSUE of this Journal the program of this year's Clinical Congress was outlined in brief. In this issue, general and specialty sessions, and film programs will be outlined. In subsequent issues, Postgraduate Courses and titles of Forum reports will be published.

The Ciné Clinics, since their introduction in 1950, have become one of the outstanding features of the Clinical Congress. These film lectures demonstrate in color major points of technique which would be difficult or impossible to show otherwise. Operating surgeons will be present to discuss procedures for which they are noted. The Surgical Products Division of American Cyanamid Company, Danbury, Connecticut, sponsors the Ciné Clinics, to be presented Monday through Thursday. The following advance schedule lists the operation and operating surgeon. Participants who will discuss each film will be listed in the program.

Extrophy of the Bladder. TAGUE CHISHOLM, Minneapolis.
Parotidectomy. ALEXANDER W. ULIN, Philadelphia.
Gastric Ulcer. ROBERT E. L. BERRY, Ann Arbor.
Gastric Carcinoma. FREDERICK W. PRESTON, Chicago.
Achalasia. PAUL NEMIR, JR., Philadelphia.
Hiatus Hernia and Esophagitis. EDWARD R. WOODWARD, Gainesville.
Upper Gastrointestinal Hemorrhage. JOHN J. FARRELL, Miami.
Diverticulitis. BENTLEY P. COLCOCK, Boston.
Regional Enteritis. R. KENNEDY GILCHRIST, Chicago.
Two-Team Combined Abdominal Perineal Resection. JONATHAN E. RHOADS, Philadelphia.
Carcinoma of Colon. L. KRAEER FERGUSON, Philadelphia.
Ulcerative Colitis. JOHN VAN PROHASKA, Chicago.
Radical Pelvic Surgery. EUGENE M. BRICKER, St. Louis.
Abdominal Trauma. WILLIAM A. ALTEMEIER, Cincinnati.
Thyroidectomy. ALLAN D. MCKENZIE, Vancouver.
Carcinoma of the Breast. ANTHONY R. CURRERI, Madison.
Varicose Veins. JOHN L. KEELEY, Chicago.
Free Skin Grafts. JAMES BARRETT BROWN, St. Louis.
Carcinoma of Pancreas. HAROLD A. ZINTEL, New York.
Gallbladder Disease. CHARLES B. PUESTOW, Chicago.

On Tuesday evening, the popular Symposium on Spectacular Problems in Surgery will be presented. The advance schedule follows:

Electrical Narcosis. JAMES D. HARDY, Jackson, Mississippi.
Cardiac Hematoma. DENTON A. COOLEY, Houston.
Turban Tumor of the Scalp. GLENN A. YOUNG, Long Beach.
Endoscopic Photography of the Common Duct. ELLIOTT S. HURWITT, New York.
Hyperaldosteronism. EDWIN H. ELLISON, Milwaukee.
Resection of Tumors of the Liver. WILLIAM P. LONGMIRE, JR., Los Angeles.
Giant Emphysematous Bleb of the Lung. ALTON OCHSNER, New Orleans.
Resection of Aneurysm of the Renal Artery. GEORGE C. MORRIS, JR., Houston.

Paul V. Harper, Chicago, and Edwin H. Ellison, Milwaukee, local and national chairman, respectively, of the television program, have planned an interesting series of operations to be televised from Albert Merritt Billings Hospital at the University of Chicago.

## *General Sessions*

Sessions open Monday morning with Francis D. Moore moderating a panel on "Management of Late Peritoneal Sepsis," assisted by panelists John M. Kinney, Champ Lyons, and John H. Mulholland.

The first afternoon panel is entitled "Complications of Cholelithiasis" moderated by Bentley P. Colcock, with panelists Charles W. McLaughlin, Jr., E. Lee Strohl, and John M. Waugh. The Baxter Lecture will follow on "Control of Effective Volume and Tonicity; Body Composition in Surgery," given by Francis D. Moore. The final panel, moderated by B. Marden Black, is "Place of Surgery in Treatment of Thyroid Disease," with panelists Oliver Cope, Brown M. Dobyns, and Howard Mahorner.

A special panel entitled "Impartial Medical Testimony" will be heard Tuesday morning with Preston A. Wade as moderator, and speakers Richard J. Bennett, Howard Reid Craig, and Aron Steuer. Afternoon sessions open with "Operative and Postoperative Cardiopulmonary Crises," James V. Mahoney, Jr., moderator, and panelists Denton A. Cooley, John H. Gibbon, Jr., Dwight C. McGoon, and Frank Cole Spencer. Harrison L. McLaughlin, Chairman of the Committee on Trauma, will preside at the Trauma Symposium which follows. Topics and speakers are:

Tetanus Prophylaxis. HOWARD E. SNYDER.
The Present Status of Plastic Polymers in Fracture Treatment. THOMAS B. QUIGLEY.
Prevention and Care of Athletic Injuries. DON H. O'DONOGHUE.
Causes of Death Following Trauma. WILLIAM T. FITTS, JR.

"Tumors of the Colon," the final afternoon panel, is moderated by Jonathan E. Rhoads. Speakers are Isidore Cohn, Jr., Carl A. Moyer, Claude E. Welch, and Roger Wilson.

Wednesday afternoon, C. Stuart Welch moderates "Diagnosis and Management of Diseases of the Spleen" with William Dameshek, Edwin H. Ellison, H. Rocke Robertson, and Orvar Swenson discussing. The cancer panel "Alterations in the Hormonal Balance of the Cancer Patient" follows. Moderated by R. Lee Clark, it has as panelists: Donald D. Matson, Willet F. Whitmore, Jr., B. J. Kennedy, and Willard H. Parsons. The Trauma Oration which follows will be presented by Preston A. Wade and is entitled "The Specialist and the Injured Patient." The Oration is followed by a trauma panel "Emergency Department Problems in Trauma" moderated by Robert H. Kennedy. Participants are Oscar P. Hampton, Jr., Frank P. Patterson, and Ernest C. Shortliffe. Wednesday's panel sessions end with "The Surgery of Duodenal Ulcer" moderated by H. William Scott, Jr. Panelists are Lester R. Dragstedt, Joseph B. Kirsner, Ian B. MacDonald, and Owen H. Wangensteen.

Thursday's program has one afternoon panel, "Regional Perfusion of Cancer," moderated by Oscar Creech, Jr., with speakers Cecil M. Couves, Donald B. Rochlin, William W. Shingleton, and John S. Stehlin, Jr. This afternoon program will be completed with the Martin Memorial Lecture followed by the annual meeting of Fellows.

What's New in Surgery, a résumé of the Forum reports heard all week, will be held Friday morning, with William P. Longmire, Jr. presiding, and the following speakers:

Neurological Surgery. WILLIAM H. SWEET.
Gastrointestinal Biliary Conditions. EDWARD R. WOODWARD.
Plastic Surgery. TRUMAN G. BLOCKER.
Tumors. WILLIAM D. HOLDEN.
Anesthesia and Pulmonary Problems. WILLIAM S. BLAKEMORE.
Cardiovascular Surgery. C. ROLLINS HANLON.
Orthopedic Surgery. WILLIAM STANLEY SMITH.
Nutrition and Body Fluids, Shock, and Burns. BERNARD ZIMMERMANN.
Obstetrics and Gynecology. E. STEWART TAYLOR.

## *Specialty Panel Discussions*

The preliminary program for these sessions follows:

### OBSTETRICS AND GYNECOLOGY

MONDAY—Immunologic Aspects of Gynecological and Obstetrical Conditions. S. LEON ISRAEL, Moderator. Panelists: SAMUEL J. BEHRMAN, PHILIP LEVINE, JOHN B. GRAHAM, RONALD R. GREENE, and SAUL B. GUSBERG. Management of Unsuspected Genital Malignancies Diagnosed Shortly After Pelvic Operations. JOE V. MEIGS, Moderator. Panelists: CONRAD G. COLLINS, GEORGE H. GARDNER, and CHARLES L. MARTIN. Present Status of

Early Diagnosis of Uterine Cancer. WILLIAM N. THORNTON, JR., Moderator. Panelists: HOWARD ULFELDER, T. N. EVANS, and JAMES W. REAGAN.

TUESDAY—Viral Infections in Pregnancy: Maternal Aspects. KEITH P. RUSSELL, Moderator. Panelists: GEORGE G. JACKSON, W. PAUL HAVENS, JR., and JOHN C. ULLERY. Viral Infections in Pregnancy: Fetal Aspects. WILLIAM F. MENGERT, Moderator. Panelists: MARK H. LEPPER, and other participants to be announced.

THURSDAY—Prevention and Management of Abortion. JASON H. COLLINS, Moderator. Panelists: ROBERT H. BARTER, WILLIAM B. MCGEE, and SEWARD H. WILLS.

FRIDAY—Management of Genital Fistulas. LANGDON PARSONS, Moderator. Panelists: JOSEPH H. PRATT, JUSTIN J. CORDONNIER, and HENRY C. FALK. Extragenital Surgical Lesions During Pregnancy. JOHN C. WEED, Moderator. Panelists: WALTER F. BECKER, ROBERT S. SPARKMAN, J. HARVEY JOHNSTON, JR., and RALPH E. DOLKART.

### PLASTIC SURGERY

MONDAY—Use and Abuse of Skin Grafts. STEPHEN R. LEWIS, Moderator. Panelists: ROSS H. MUSGRAVE, WILLIAM K. LINDSAY, and NICHOLAS G. GEORGIADE. Use and Abuse of Skin Flaps. JOHN W. CURTIN, Moderator. Panelists: JOSEPH R. CONNELLY, GEORGE F. CRIKELAIR, and JAMES H. HENDRIX, JR.

### UROLOGY

MONDAY—Reconsideration of Surgical Renal Hypertension. EUGENE F. POUTASSE, Moderator. Panelists: JOHN T. MACLEAN, EARL E. EWERT, and J. HOWARD PAYNE.

TUESDAY—Surgical Management of Benign Bladder Neck Obstruction in the Adult. ROBERT LICH, JR., Moderator. Panelists: WILLIAM A. MILNER, JOSEPH H. KIEFER, and ROBERT T. PLUMB.

WEDNESDAY—The Problems Associated with Micturition. DAVID A. CULP, Moderator. Panelists: WILLIAM L. VALK, JACK LAPIDES, and IAN THOMPSON.

FRIDAY—Differential Diagnosis and Management of Tumors of the Kidney. EDWIN P. ALYEA, Moderator. Panelists: ROBERT A. GARRETT, CHARLES A. HULSE, and T. BRENT WAYMAN.

### OPHTHALMIC SURGERY

WEDNESDAY, afternoon—Ophthalmic Surgery Symposium. FRANK W. NEWELL, Moderator. Present Status of Retinal Detachment Surgery. P. ROBB MCDONALD. Present Status of Cataract Surgery. JOHN M. MCLEAN. Present Status of Glaucoma Surgery. HAROLD G. SCHEIE.

WEDNESDAY, evening—Ophthalmic Surgery Symposium. BANKS ANDERSON, Moderator. Present Status of Ocular Muscle Surgery. GOODWIN M. BREININ. Present Status of Ptosis Surgery. JOHN W. HENDERSON. Present Status of Surgery of the Lids and Orbit. VIRGIL G. CASTEN.

### OTORHINOLARYNGOLOGY

FRIDAY—Management of Laryngeal Injuries. KENNETH C. JOHNSTON, Moderator. Panelists: DANIEL C. BAKER, JR., CHARLES M. NORRIS, and WALTER P. WORK. Management of Facial Injuries. WILLIAM C. HUFFMAN, Moderator. Panelists: JOSEPH R. RONGETTI, JEROME A. HILGER, and G. SLAUGHTER FITZ-HUGH. Tumors of the Ear and Temporal Bone. FERNAND MONTREUIL, Moderator. Panelists: JOHN S. LEWIS, GEORGE A. SISSON, and WILLIAM M. TRIBLE. Microsurgery of the Ear. JOHN R. LINDSAY, Moderator. Panelists: RICHARD J. BELUCCI, SHIRLEY HAROLD BARON, and THEODORE E. WALSH.

### NEUROLOGIC SURGERY

FRIDAY—Cerebral Vascular Insufficiency. EDWIN B. BOLDREY, Moderator. Panelists: RICHARD L. DESAUSSURE, JR., HARRY A. KAPLAN, RICHARD C. SCHNEIDER, and KEASLEY WELCH. Complications of Neurosurgical Diagnostic Procedures. ROBERT A. GROFF, Moderator. Panelists: W. JAMES GARDNER, FRANK J. OTENASEK, BERTRAM SELVERSTONE, and BENJAMIN B. WHITCOMB. Head Injuries, Symposium. JEFFERSON BROWDER, Moderator. Panelists: Special Problems of Head Injury in Childhood, EBEN ALEXANDER. Traumatic Intracranial Hemorrhage, ALBERT W. COOK. Hypothermia, CHARLES G. DRAKE. Pathogenesis of Cerebral Edema, JOSEPH P. EVANS. Comparative Data on Agents to Reduce Intracranial Pressure, ROBERT G. FISHER.

### THORACIC SURGERY

FRIDAY—Recent Advances in Cardiac Surgery, WILLIAM H. MULLER, JR., Moderator. Panelists: ANDREW G. MORROW, EARLE B. KAY, and JOHANN L. EHRENHAFT. Postoperative Problems in Thoracic Surgery. JOHN W. STRIEDER, Moderator. Panelists: ROBERT R. SHAW, JOHN B. GROW, and EDWARD A. GAENSLER.

## *Martin Lecture and Fellows' Meeting*

Admiral Hyman G. Rickover will give the Martin Memorial Lecture on Thursday afternoon, 5 October, at 3:15. The Annual Meeting of Fellows of the College will follow at 4:00 o'clock. In addition to the election of officers and Governors, there will be announcements and reports from officials. All Fellows are urged to attend.

## *Graduate Training Symposium*

Robert M. Zollinger will preside over a symposium on basic surgical training on Thursday from 1:30 to 3 p.m.

### *Advance Registration*

Clinical Congress forms for advance registration, hotel accommodations, Postgraduate Courses, and transportation have been included in the invitation brochure already mailed to Fellows. Early return of these forms is advisable to assure prompt receipt of your badge upon arrival, early choice of Postgraduate Courses, satisfactory hotel or motel accommodations, and travel information. Non-Fellows may obtain this brochure by writing to the College, 40 East Erie Street, Chicago 11.

### *Fees*

Fellows whose dues are paid to 31 December 1960 pay no registration fee; those whose dues are not paid as of above date pay $40.00. Non-Fellows will pay $40.00 if registered Sunday, Monday, or Tuesday; $30.00 if registered Wednesday; $20.00 if registered Thursday; $10.00 if registered Friday. Members of the Federal services will pay half of the above schedule of fees. No fee, except for Postgraduate Courses, is required of Initiates, members of the Candidate Group, and surgical residents. Everyone attending a Postgraduate Course pays a fee of $10.00. It is particularly requested that everyone wishing to attend carry identification cards—Fellowship, Candidate, Initiate—to expedite the registration process. Registration is limited to doctors of medicine.

### *Registration Hours*

Registration Hours at the Conrad Hilton will be:

SUNDAY, 1 October, 3 p.m. to 7:30 p.m.
MONDAY, 2 October, 8 a.m. to 5:30 p.m.
TUESDAY, 3 October, 8:15 a.m. to 5 p.m.
WEDNESDAY, 4 October, 8:15 a.m. to 5 p.m.
THURSDAY, 5 October, 8:30 a.m. to 5 p.m.
FRIDAY, 6 October, 8:30 a.m. to 5 p.m.

### *Ladies' Entertainment*

Wives attending will find much to interest them in and around the Loop area. Mrs. Paul Holinger, chairman of the Ladies' Entertainment Committee, and her co-workers have planned a full week of activities. Monday afternoon, the opening day, there will be a get-acquainted tea. Other events include visits to the art museum, miniature opera and luncheon, a fashion show, and a lecture on interior decoration today by an authority of the American Institute of Decorators. In addition there are always shopping, concerts, theater, and sightseeing tours. Some of the new little theater clubs offer clever entertainment for evening hours. Barnes Theatre Ticket agency and Gray Line Tours will have desks in the Ladies' Hospitality Suite at The Conrad Hilton to help with plans for the week. In addition, the Ladies' Entertainment Committee will assist with any special preferences.

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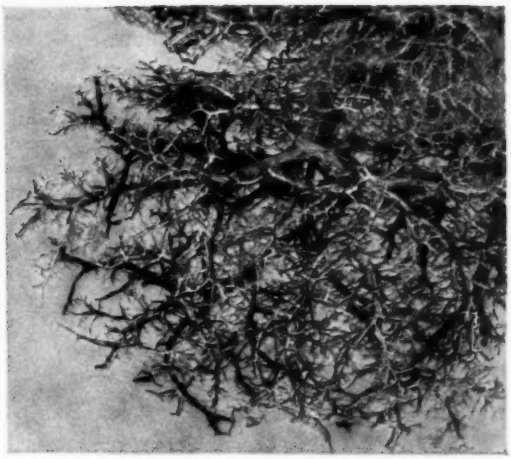

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FIG. 1. a, Close-up of a corrosion cast of a normal liver in which the vascular compartments have been injected with colored plastic material. The hepatic artery is red, the portal vein yellow, and the hepatic vein blue. b, Close-up of a cirrhotic liver taken from a patient with ascites. Note the marked reduction of the hepatic venous system, blue, as compared with the normal in "a." The portal venous system, yellow, would seem to be increased, but it is not by actual measurement.

*Changes in the Hepatic Blood Vessels in Cirrhosis of the Liver.—*
*John H. Carter, C. Stuart Welch, and Richard E. Barron.*